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The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease

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Abstract

Background. Inhibition of the renin–angiotensin–aldosterone system (RAAS) has shown to slow chronic kidney disease (CKD) progression. This is most notable at the earlier stages of diabetic and proteinuric nephropathies.

Objective. Here, we observed the impact of discontinuation of angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptors blockers (ARB) in patients with advanced kidney disease.

Methods. 52 patients (21 females and 31 males) with advanced CKD (stages 4 and 5), who attended our low clearance clinic (LCC) in preparation for renal replacement therapy (RRT). Mean age was 73.3 ± 1.8 years with an estimated glomerular filtration rate (eGFR) of 16.38 ± 1 ml/min/1.73 m^2. Baseline urine protein:creatinine ratio (PCR) was 77 ± 20 mg/mmol. 46% suffered from diabetes mellitus. Patients were followed for at least 12 months before and after ACEi/ARB were stopped.

Results. 12 months after discontinuation of ACEi/ARB eGFR increased significantly to 26.6 ± 2.2 ml/min/1.73 m^2 ($p = 0.0001$). 61.5% of patients had more than a 25% increase in eGFR, whilst 36.5% had an increase exceeding 50%. There was a significant decline in the eGFR slope −0.39 ± 0.07 in the 12 months preceding discontinuation. The negative slope was reversed +0.48 ± 0.1 ($p = 0.0001$). Mean arterial blood pressure (MAP) increased from 90 ± 1.8 mmHg to 94 ± 1.3 mmHg ($p = 0.02$), however ≥50% of patients remained within target. Overall proteinuria was not affected (PCR before = 77 ± 20 and after = 121.6 ± 33.6 mg/mmol).

Conclusion. Discontinuation of ACEi/ARB has undoubtedly delayed the onset of RRT in the majority of those studied. This observation may justify a rethink of our approach to the inhibition of the RAAS in patients with advanced CKD who are nearing the start of RRT.

Keywords: advanced CKD; angiotensin II receptor blockade; angiotensin-converting enzyme inhibition; low clearance clinic

Introduction

In view of the constant global rise in end-stage renal disease (ESRD) and the perceived increase in the number of individuals suffering from chronic kidney disease (CKD), attention has focused over the last 10 years on early detection of CKD as well as slowing its progression [1,2]. Prominent amongst interventions aimed at slowing the progression of CKD is the inhibition of the renin–angiotensin–aldosterone system (RAAS).

Over the last 20 years, a number of studies have demonstrated that inhibition of the RAAS system is extremely effective in slowing the progression of experimental and clinical CKD [3–6]. In patients with progressive CKD, most studies showing benefit of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptors blockers (ARB) focused on diabetic nephropathy and proteinuric CKD. In fact, the seminal study of ACEi in non-diabetic CKD, the REIN study, showed the benefit to take place in those suffering from nephrotic range proteinuria [7]. Further meta-analyses [8] and systematic reviews [9] suggested that ACEi/ARB treatment is beneficial in proteinuric CKD patients with proteinuria >1 g/24 h and 0.5 g/24 h, respectively. These data, with all their limitations, have become the evidence upon which an increasing number of CKD guidelines related to the use of ACEi/ARB have been based [10].

A critical review of the literature on ACEi/ARB in non-diabetic CKD shows a number of limitations. Most studies in non-diabetic CKD, with the exception of REIN, failed to fully dissociate the beneficial effect of RAAS blockade from its hypertensive effect [11]. Such limitations have been the subject of considerable analyses and controversy [3,12]. The meta-analyses and systematic reviews mentioned above are also unable to dissociate the two actions: anti-hypertensive from anti-progressive. This was clearly stated in another meta-analysis [13]. Furthermore, a number of reports in diabetic [14] and non-diabetic kidney disease [15–17] have hinted at the possibility of ACEi/ARB accelerating the progression of CKD. This would be expected predominantly in type 2 diabetes with diffuse macrovascular disease affecting the renal vasculature and causing ischaemic nephropathy. It would also be expected in the number of cases of CKD affecting elderly individuals suffering from diffuse atherosclerosis [18]. The latter are rapidly becoming one of the major causes of ESRD [19]. Furthermore, a recent publication (ONTARGET) highlighted the fact that in high-risk individuals, the combination of ACEi and ARB may also accelerate the decline in kidney function. This is most likely to be related to the diffuse atherosclerotic changes and renal hypoperfusion affecting individuals at a high cardiovascular risk [20].

Although one study from China suggested that it was safe to use ACEi in advanced CKD (stage 4), we have our doubts regarding the validity of the data in view of duplicate publications of this study with conflicting data [21,22]. We have also noted from our own clinical experience that a growing number of patients, mostly elderly, with acute on chronic kidney disease were on ACEi/ARB. This is in agreement with the recent report by Onuigbo and Onuigbo who claimed that ACEi/ARB accelerate CKD in a substantial number of cases [17].

With the above in mind, we decided to examine the impact of stopping ACEi/ARB in patients with CKD 4–5 who attended our advanced kidney care clinic (low clearance clinic; LCC) in preparation for renal replacement therapy (RRT). The rationale was that these patients have already progressed to ESRD and are soon to require RRT and that discontinuing a potentially nephrotoxic agent at this stage may do some good and could do no harm from the disease progression standpoint. We also considered that if renal function improved, the cardiovascular disease (CVD) risk of these patients would improve compared to those who would start RRT. We reasoned that after all, the CVD risk of those who may regress from CKD 5 to CKD 4 would be less than that of those from CKD 5 who would be treated by dialysis. Finally, we were aware that the majority of those attending our LCC were more than 65 years of age, and thus, at increased risk of ACEi/ARB-induced deterioration of kidney function.

Patients and methods

This is an observational report of 52 patients who were on ACEi or ARB (21 females and 31 males), mean age 73.3 ± 1.8 years, who were referred to the advanced kidney care clinic (low clearance clinic LCC) of the Sheffield Kidney Institute in 2005–06 in anticipation of starting RRT. The average estimated glomerular filtration rate (eGFR) was 16.38 ± 1 ml/min/1.73 m^2 at presentation to the LCC. The baseline proteinuria [urine protein:creatinine ratio (PCR)] was 77 ± 20 mg/mmol. The patients had been followed up for at least 12 months prior to referral to the LCC and up to 12–24 months after we discontinued the ACEi or ARB. A small number of patients were followed up for a longer period [median follow-up 30 months (24–54 months)].

The choice of the anti-hypertensive medication that was used to compensate for stopping inhibitors of the RAAS depended on the severity and significance of the underlying CVD and congestive cardiac failure (CCF). In patients without symptoms or overt signs of CCF, we opted for a combination of a calcium channel blocker (CCB) along with the loop diuretic that was already in place. Often the latter was slightly increased to counteract any fluid retention/oedema associated with the CCB (amlodipine). In patients with symptomatic CCF, we have replaced the inhibitor of RAAS by a combination of an oral nitrate and hydralazine. This in addition to the loop diuretics they were on. All patients were followed up monthly at the outpatient department of the Sheffield Kidney Institute with careful symptoms review and physical examination.

Blood pressure and proteinuria were analysed in detail 12 months post-ACEi/ARB stoppage. The change in eGFR ml/min/month was calculated 12 months before and after stopping ACEi/ARB (eGFR slope was calculated using 4–6 measurements over 12 months before and after stopping ACEi/ARB).

Serum creatinine was measured by the standard autoanalyser technique. eGFR was estimated by the MDRD 4 variables formula. Urine protein estimation was undertaken by a random spot urine sample upon the patient's arrival at the LCC and expressed as the urine protein:creatinine ratio (mg/mmol). Blood pressure measurements were performed routinely according to standard procedures in all patients with automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical, Tampa, FL, USA).

Statistical analysis

Data were represented as mean ± standard error of the mean (SEM). The paired *t*-test and the Mann–Whitney *U*-test were used as appropriate. A P value of < 0.05 was considered statistically significant.

Table 1. Renal functional characteristics of study groups

	12 months before ACEi/ ARB were stopped	When ACEi/ARB were stopped	12 months after ACEi/ ARB were stopped	Significance
eGFR all groups (ml/min/1.73 m^2)	22.9 ± 1.4[a] ml/min/1.73 m^2	16.38 ± 1 ml/min/1.73 m^2	26.6 ± 2.2[b] ml/min/1.73 m^2	a (P = 0.0001) b (P = 0.0001)
eGFR all diabetics (ml/min/1.73 m^2)	22.7 ± 1.7[a] ml/min/1.73 m^2	15.5 ± 1.3 ml/min/1.73 m^2	23.9 ± 3.3[b] ml/min/1.73 m^2	a (P = 0.0001) b (P = 0.01)
eGFR all non-diabetics (ml/min/1.73 m^2)	23.2 ± 2.2[a] ml/min/1.73 m^2	17.5 ± 1.7 ml/min/1.73 m^2	28.6 ± 2.9[b] ml/min/1.73 m^2	a (P = 0.01) b (P = 0.001)
Total change in eGFR slope	−0.39 ± 0.07		+0.48 ± 0.1	P = 0.0001
eGFR rate of change for patients who improved >25% (ml/min/month)	−0.49 ± 0.1 ml/min/month		+0.95 ± 0.1 ml/min/month	P = 0.0001
eGFR slope for patients who improved > 25%	−0.5 ± 0.1		+0.78 ± 0.1	P = 0.0001
eGFR rate of decline for patients who deteriorated >25% (ml/min/month)	−0.06 ± 0.1 ml/min/month		−0.2 ± 0.1 ml/min/month	P = 0.01
eGFR slope for patients who deteriorated >25%	−0.05 ± 0.1		−0.6 ± 0.1	P = 0.01
eGFR rate of decline for patients who remained unchanged (ml/min/month)	−0.14 ± 0.1 ml/min/month		−0.11 ± 0.1 ml/min/month	NS
eGFR slope for patients who remained unchanged	−0.13 ± 0.06		−0.12 ± 0.06	NS

eGFR, estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptors blockers.

Results

General observations

Of the 52 patients, 5 were assumed to have renovascular disease based on a history of diffuse atherosclerosis and the presence of vascular bruits on physical examination; two of the five had ultrasonography showing significant asymmetry between kidney size. It is not our practice at the Sheffield Kidney Institute to pursue the investigations of such patients by magnetic renal angiography (MRA) unless blood pressure control is not achieved by medical treatment. Further, the use of gadolinium-containing contrast material is nowadays contraindicated in patients with advanced renal insufficiency. Of the 52 patients, 24 (46%) had diabetes mellitus, mostly type 2, and the remainder had a range of nephropathies including chronic glomerulonephritis (n = 3), chronic tubulo-interstitial nephritis (n = 1), 5 with presumed atherosclerotic renovascular disease, 2 with obstructive uropathy, 1 with multiple myeloma and 10 with small kidneys of unknown aetiology. Of the 52 patients, 35 (67%) were hypertensive, treated on average by three anti-hypertensive medications including ACEi or ARB and 7 patients had CCF. At 12 months after stopping ACEi or ARB, the majority of CKD patients had no significant onset or exacerbation of CVD-related symptoms or signs. Four patients out of seven who had significant CCF (NYHA class III or above) developed transient worsening of their symptoms, mainly exertional dyspnoea. This was addressed, to good effect, by a further increase in their diuretic therapy. Five patients (9.6%) reached ESRD and were started on dialysis. Five patients died [the causes of death were secondary to multiple myeloma (1), pneumonia (1), CCF (2), and unknown (1)].

Effect of stoppage of ACEi/ARB on eGFR

The average eGFR when ACEi/ARB were stopped was 16.38 ± 1 ml/min/1.73 m^2, which increased significantly to reach 26.6 ± 2.2 ml/min/1.73 m^2 (P = 0.0001) 12 months after stopping ACEi/ARB. The same observation (significant rise in eGFR) was noticed when the group was divided into diabetic and non-diabetic patients (Table 1). A total of 61.5% of patients had a more than 25% increase in eGFR at 12 months after ACEi/ARB were stopped. This persisted in most up to 24 months (Figure 1). Of note, 36.5% had an increase in eGFR exceeding 50% at 12 months. Limited number of cases (n = 6) who were followed up for a longer period showed that the improvement was sustained for up to 54 months (Figure 2). Furthermore, 25% and 19% of patients changed their CKD stages from stage 5 to 4 and from stage 4 to 3, respectively. Subsequently, some of these were discharged from the renal clinics.

There was a significant decline in the eGFR against time slope in the 12 months preceding the discontinuation of ACEi/ARB (−0.39 ± 0.07). The decline in eGFR was reversed 12 months after stopping ACEi/ARB (+0.48 ± 0.1), (P = 0.0001).

The whole observation group was divided into three subgroups: Group 1, patients whose renal function improved significantly (increase eGFR >25%); they were the majority of those studied, 32/52 (61.5%) whose eGFR rate of declined was reversed from −0.49 ± 0.1 to +0.95 ± 0.1 ml/min/month (P = 0.0001). Group 2, patients whose eGFR of decline deteriorated by >25%, 4 of 52 (7.69%) as their eGFR of decline accelerated from −0.06 ± 0.1 to −0.2 ± 0.1 ml/min/month (P = 0.01). Group 3, patients whose eGFR of decline remained unchanged after stop-

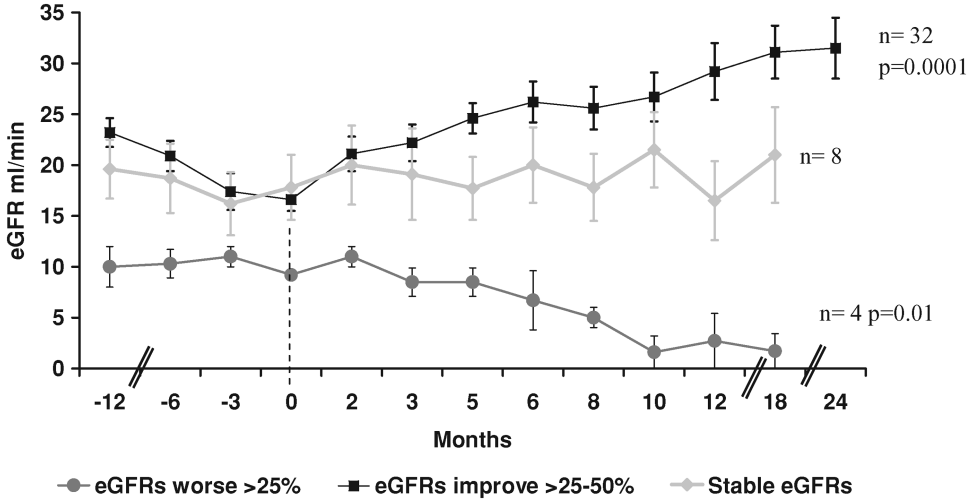

Fig. 1. Changes in eGFR after stopping ACEi/ARB in patients with advanced CKD. Data presents changes as mean eGFR ± SEM in patients with advanced CKD up to 24 months after stopping ACEi/ARB.

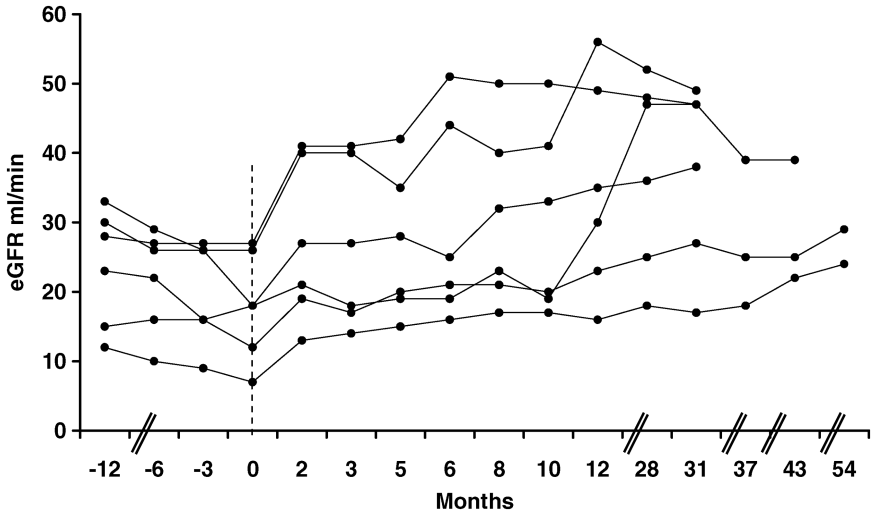

Fig. 2. Example of the course of selected patients with sustained improvement in eGFR (>25%) up to 54 months after stopping ACEi/ARB. Data presents changes as mean eGFR in selected patients with advanced CKD.

ping of ACEi/ARB, 8 of 52 (15.3%) (−0.14 ± 0.1 and −0.11 ± 0.1 ml/min/month) (Table 1 and Figure 1). The respective changes in eGFR against time slope in the three groups were as follows: Group 1: eGFR against time slope before discontinuation of ACEi/ARB: −0.5 ± 0.1 and after: +0.78 ± 0.1 (P = 0.0001), Group 2: slope before: −0.05 ± 0.1 and eGFR slope after: −0.6 ± 0.1 (P = 0.01), Group 3: eGFR against time slope before discontinuation of ACEi/ARB: −0.13 ± 0.06 and after: −0.12 ± 0.06.

Effect of discontinuation of ACEi/ARB on blood pressure control

Blood pressure control [systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP)] changed 12 months after stopping ACEi/ARB; SBP increased from 134 ± 3 to 139 ± 2.2 mmHg (P = 0.04), DBP from 69 ± 1.7 mmHg to 72 ± 1.4 mmHg (P = 0.04) and MAP from 90 ± 1.8 mmHg to 94 ± 1.3 mmHg (P = 0.02), respectively. However, 53% (n = 27/51) of patients had blood pressure levels within recommended targets (<130/80 mmHg) 12 months before and after stopping ACEi/ARB (Table 2).

Effect of discontinuation of ACEi/ARB on proteinuria

Overall, proteinuria was not significantly affected by stopping ACEi/ARB (from 77 ± 20 to 121.6 ± 33.6 mg/mmol). Even when we divided patients into those who had significant proteinuria (>50 mg/mmol) before discontinuation, there was no significant increase found 12 months after stopping ACEi/ARB when compared to

Table 2. Comparisons of clinical variables between groups

	12 months before ACEi/ ARB were stopped	When ACEi/ARB were stopped	12 months after ACEi/ ARB were stopped	Significance
SBP (mmHg)		134 ± 3 mmHg	139 ± 2.2 mmHg	$P = 0.04$
DBP (mmHg)		69 ± 1.7 mmHg	72 ± 1.4 mmHg	$P = 0.04$
MAP (mmHg)		90 ± 1.8 mmHg	94 ± 1.3 mmHg	$P = 0.02$
Urine Protein:creatinine ratio (PCR) (mg/mmol)	79.5 ± 24.1 mg/mmol	77 ± 20 mg/mmol	121.6 ± 33.6 mg/mmol	NS
Urine PCR for diabetics	97.5 ± 36.2 mg/mmol	110.4 ± 38.3 mg/mmol	135.7 ± 48.2 mg/mmol	NS
Urine PCR for non-diabetics (mg/mmol)	62.2 ± 32.5 mg/mmol	51.3 ± 16 mg/mmol	108 ± 47.6 mg/mmol	NS
PCR >50 mg/mmol at discontinuation	161.9 ± 44.3 mg/mmol	161 ± 36.5 mg/mmol	239.3 ± 60.4 mg/mmol	NS
PCR <50 mg/mmol at discontinuation	8.4 ± 3 mg/mmol	10.3 ± 2.9 mg/mmol	10.9 ± 2.5 mg/mmol	NS

SBP, systolic blood pressure; DBP, diastolic blood pressure, MAP, mean arterial blood pressure; PCR, protein:creatinine ratio.

baseline levels. Also, when we analysed the proteinuria pattern in diabetic and non-diabetic CKD patients, we failed to observe a significant change upon discontinuation of ACEi/ARB (Table 2).

Discussion

This is the first observation, to our knowledge of a systematic discontinuation of ACEi/ARB in patients with advanced CKD (eGFR mostly <20 ml/min/1.73 m^2). It was prompted by anecdotal observations made by our group and a rationale that discontinuation of agents that can cause up to 30% decrease in eGFR may be beneficial in patients on the verge of starting dialysis treatment. This was not a randomized clinical trial but instead the report of an observation made of a clinical decision we took in a high-risk group of patients who mostly reached ESRD (CKD stage 5). It showed a significant overall increase in eGFR with some patients showing >50% increase from the value at the time of discontinuation of ACEi/ARB. It also led a number of patients who were about to start RRT to have a longer time before such treatment was required. Few patients improved to the extent that they were discharged from the renal services back to their general practitioner.

Upon stopping ACEi/ARB, we expected that some patients may have a 20–25% increase in eGFR, but did not expect higher increments. We were not even sure whether at this late stage of CKD there would be scope for any reversibility of kidney function. There could have been reservations that discontinuation of the ACEi/ARB may accelerate the decline of kidney function, but we observed the opposite. We clearly attempted to compensate for having stopped ACEi/ARB by increasing the patient's alternative anti-hypertensive agents. However, there was a small but statistically significant increase in BP after stopping RAAS inhibitors. However, the overall percentage of patients achieving target levels (<130/80 mmHg) was comparable before and after discontinuation.

We were also concerned that discontinuing the ACEi/ARB may exacerbate proteinuria, although this was a lesser concern bearing in mind that for those who reached ESRD, we reasoned that the control of proteinuria was less relevant. Further, many were still significantly proteinuric in spite of being on ACEi/ARB. There was no difference in the severity of proteinuria on and off ACEi/ARB. This may reflect that by stage 5 CKD, the impact of ACEi/ARB on proteinuria 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 RAAS. Also, a tubular component to the proteinuria reflecting extensive tubulo-interstitial damage at this stage of CKD would not be affected by ACEi or ARB [23]. On the other hand, the overall renal functional improvement, after stopping ACEi/ARB, may reflect the improved function of the least affected remaining functioning glomeruli through restoration of remnant glomerular hyperfiltration.

Of interest, patients who seemed to benefit most from stopping ACEi/ARB were those whose kidney function was declining in spite of ACEi/ARB treatment. This took place in diabetic and non-diabetic nephropathies. This is consistent with observations made that such treatment may contribute to the faster rate of decline [14].

Finally, concern has been expressed that discontinuation of cardioprotective agents such as ACEi/ARB may be detrimental to CKD patients known to be at a high CVD risk [24]. There was no apparent harm as patients who complained of worsening heart failure were managed by increasing diuretics or alternate vasodilators including nitrates and hydralazine. We also reasoned that CVD would be improved rather than worsened by improved kidney function and avoidance of dialysis therapy. In this pilot observation, there was no short-term evidence that discontinuation of ACEi/ARB had a significant short-term adverse cardiovascular effect as far as exacerbating signs or symptoms of congestive heart failure in the majority of patients.

There is no doubt that this is a small, anecdotal, report of improved kidney function in patients with ESRD who were about to start RRT. Discontinuation of ACEi/ARB has undoubtedly delayed the onset of RRT in the majority of those studied. This observation may justify a rethink of our approach to the inhibition of the RAAS in patients

with advanced CKD who are approaching RRT or in those who we may consider conservative management. Also, it would be useful to know whether some clinical or functional characteristics can predict those who would improve after discontinuation of ACEi/ARB as well as those who may worsen.

Conflict of interest statement. None declared.

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