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Analytical Review of the Evidence for Renoprotection by Renin-Angiotensin-Aldosterone System Blockade in Chronic Kidney Disease – A Call for Caution

Macaulay A. Onuigbo

Midelfort Clinic, Mayo Health System, Eau Claire, Wisc., USA

Key Words
Angiotensin-converting enzyme inhibitors · Renin-angiotensin-aldosterone system blockade · Renoprotection

Abstract
Despite reported renoprotection with angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and notwithstanding their increased use, we continue to experience an epidemic of acute renal failure (ARF)/chronic kidney disease/end-stage renal disease. Consequently, concerns about iatrogenic renal failure have resurfaced. Different analysis of these trials revealed flaws such as recruitment of relatively younger patients with preserved baseline renal function, common utilization of lower end doses of ACEIs/ARBs, high drug discontinuation rates, excessive use of surrogate endpoints, inadequate reporting of adverse effects, and short duration studies. Again, lower 24-hour ambulatory blood pressure among patients in the ramipril arm of the micro-HOPE (Heart Outcomes Prevention Evaluation) study raises doubts of renoprotection beyond blood pressure lowering. The disappointing results from the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) study only compounded these doubts. We demonstrated significant renal salvage after ACEI/ARB was discontinued in chronic kidney disease patients recruited with increasing ARF while on ACEI/ARB. Apart from our reports, there are increasing reports incriminating the use of ACEI/ARB with ARF exacerbations. We conclude that close and indefinite monitoring of estimated glomerular filtration rate is an absolute must in these patients. The treating physician must be ready to consider trial discontinuation of ACEI/ARB, promptly. Combination ACEI + ARB therapy should be the exception, rather than the rule. Temporary withdrawal of ACEI/ARB before certain exposures, 'renoprevention', would only further improve the results of renoprotection.

Since the mid 1990s, an evidence-based consensus has emerged of enhanced renoprotection with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), beyond blood pressure (BP) lowering, in diabetic and nondiabetic nephropathies, with and without hypertension [1] (table 1). As a result, the last 2 decades have witnessed an escalating use of renin-angiotensin-aldosterone system (RAAS) blocking agents in clinical medicine [2]. Despite this widening application of RAAS blocking strategies in the US, during the past 2 decades, the incidence of acute renal failure

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Macaulay A. Onuigbo, MD, MSc
Midelfort Clinic, Mayo Health System
1221 Whipple Street
Eau Claire, WI 54702 (USA)
Tel. +1 71 58 383 891, Fax +1 71 58 381 946, E-Mail onuigbo.macaulay@mayo.edu

Table 1. A critical appraisal of the large randomized RAAS blockade trials (all reported p values are 2-sided)

Trial (publication year)	Study size n	Mean age years	Trial drug vs. placebo/other	Indication for trial drug	Discontinuation rates, trial drug vs. placebo/other, %
Collaborative Study Group (1993) [23]	409	35	Captopril (207) vs. placebo (202)	Renoprotection in IDDM + proteinuria	not reported
Micro-HOPE (2000) [24]	3,577	65	Ramipril vs. placebo	CV and renoprotection in adult hypertensive DM	23 vs. 29.3
IDNT (2001) [25]	1,715	59	Irbesartan (579) vs. amlodipine (567)	Renoprotecion in Type 2 DM	23.7 (overall)
IDNT (2001) [25]	1,715	59	Irbesartan (579) vs. placebo (569)	Renoprotecion in Type 2 DM	23.7 (overall)
RENAAL (2001) [26]	1,513	60	Losartan (751) vs. placebo (762)	Renoprotection in Type 2 DM	53.5 vs. 46.5
ALLHAT (2005) [9]	9,054 vs. 9,048 vs. 15,255	67	Lisinopril vs. amlodipine vs. chlorthalidone	CV and renoprotection in high-risk hypertensives	3.5
ONTARGET (2008) [19]	8,576 vs. 8,542 vs. 8,502	66	Ramipril vs. telmisartan vs. combination Rx	CV protection in high-risk patients	24.5 vs. 23 vs. 29.3 p = 0.001

(ARF)/chronic kidney disease (CKD)/end-stage renal disease (ESRD) especially among US diabetics and the elderly has continued to increase; a rate of increase that had outpaced the rate of increase of the diabetes epidemic [3–7]. The incidence of ARF in US hospitalized patients continues to escalate, with recent data from the US Centers for Disease Control showing even more worrisome escalations in first-listed discharge diagnosis of ARF, especially among US adults aged ≥65 years [3]. Furthermore, there is increasing evidence for a similarly rising incidence of community-acquired ARF, both dialysis requiring and nondialysis requiring, in the USA, in the same time line, the explanation of which remains unknown [4]. Also, as recently as March 2007, the authoritative Morbidity and Mortality Weekly Report of the US Centers for Disease Control determined that 16.8% of the US population aged ≥20 years had CKD, according to 1999–2004 National Health and Nutrition Examination Survey (NHANES) database, compared with 14.5% from the 1988–1994 NHANES (i.e., NHANES III) database [5]. Finally, by most estimates, over the last 2 decades, we have continued to experience an ever-increasing ESRD epidemic here in the US [6]. Given an ageing US population, this concordance of epidemiological observations has raised a specter of iatrogenic renal failure from the use of these agents [7]. Outstandingly in 2005, Jones et al. [7], after an analysis of time trends in data from the United States Renal Data system, the Diabetes Surveillance Program of the Centers for Disease Control and Prevention and the general diabetes literature, demonstrated that the recent growth of the number of individuals with diabetes accounted for <10% of the increase in the number of diabetes-related ESRD. Otherwise, Jones et al. [7] surmised that most of this growth in ESRD was due to a 3-fold increase in risk of ESRD in people with diabetes which qualified as an epidemic. The same authors had hypothesized that the steep increase in ESRD cases in the US followed the explosion in the use of ACEIs since 1993, after the publication of The Collaborative Study Group paper on the protective effect of captopril in diabetic nephropathy [7].

A meta-analysis by Casas et al. [8] in 2005 of randomized, controlled, parallel-design trials, comparisons of ACEIs or ARBs with other antihypertensive drugs yielded a relative risk (RR) of 0.71 (95% CI 0.49–1.04) for doubling of creatinine with a small benefit on ESRD (RR 0.87, 95% CI 0.75–0.99). Also, in patients with diabetic nephropathy, no benefit was demonstrated in comparative trials of ACEIs or ARBs on the doubling of creatinine (RR 1.09, 95% CI 0.55–2.15), ESRD (RR 0.89, 95% CI 0.74–1.07), glomerular filtration rate (GFR) or creatinine amounts [8]. Casas et al. [8] concluded that the benefits of ACEIs or ARBs on renal outcomes in placebo-controlled trials probably resulted from a BP-lowering effect and that in patients with diabetes, additional renoprotection beyond BP lowering is unproven, and that there is

Follow-up months	Baseline mean serum creatinine mg/dl	Doubling of serum creatinine/ renal impairment, trial drug vs. placebo/other, %	ESRD/dialysis rate, trial drug vs. placebo/other, %	All-cause mortality, trial drug vs. placebo/ other, %
36	1.3	12 vs. 21, p = 0.02	9.6 vs. 15.3, p = 0.11	3.0 vs. 6.9, p = 0.11
54	1.1	6.5 vs. 8.4, p = 0.027	0.5 vs. 0.5, p = 0.7, NS	10.8 vs. 14, p = 0.004
31	1.7	16.9 vs. 25.4, p = 0.006	14.2 vs. 18.3, p = 0.07, NS	15 vs. 14.6, p = 0.9, NS
31	1.7	16.9 vs. 23.7, p = 0.005	14.2 vs. 17.8, p = 0.1, NS	15 vs. 16.3, p = 0.6, NS
41	1.9	21.6 vs. 26, p = 0.05	19.6 vs. 25.5, p = 0.007	21 vs. 20.3, p = 0.8, NS
59	1.0	not reported	2.0 vs. 2.2 vs. 1.8, p = 0.38, NS	not reported
56	1.1	0.7 vs. 0.8 vs. 1.1, p < 0.001	0.6 vs. 0.6 vs. 0.8, p = 0.1	11.8 vs. 11.6 vs. 12.5, p = 0.2, NS

uncertainty about the greater renoprotection seen in nondiabetic renal disease. The meta-analysis by Casas et al. [8] has come under very heavy criticism from proponents of more RAAS blockade with the argument that the results of this meta-analysis were too weighted against ACEIs because of the inclusion of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) data. However, we would like to counter this criticism with the following observation – a subgroup analysis of the ALLHAT diabetic population revealed that more patients in the lisinopril group did in fact progress to ESRD, when compared to the chlorthalidone group (25/1,563 vs. 26/2,755; p = 0.05, RR 1.74, 95% CI 1.00–3.01) [9]. Remarkably, this important albeit unexpected observation did not receive much press following the publication of the ALLHAT study. This subgroup observation in the ALLHAT report is indeed very eerily similar to the subsequent observations by Suissa et al. [10]. Suissa et al. [10], in a population-based historical cohort analysis of 6,102 Canadian diabetic patients with a mean age of 66 years, had revealed an increased rate ratio of ESRD of 4.2 (95% CI 2.0–9.0) after 3 years, or longer, of ACE inhibition.

On the other hand, as already acknowledged earlier in this paper, over the last 2 decades, a generally accepted consensus has emerged of enhanced renoprotection with ACEIs and ARBs, beyond BP lowering, in both diabetic and nondiabetic nephropathies, with and without hypertension [1] (table 1). In the last decade, 3 meta-analysis reports of patient-level data carried out by the ACE Inhibition in Progressive Renal Disease Study Group (AIPRD Study Group), on a total of 11 previously randomized controlled trials, have consistently demonstrated that ACE inhibition in 1,860 pooled nondiabetic patients remained beneficial after adjustment for BP and urine protein excretion (RR 0.67, 95% CI 0.53–0.84) [11–13]. They also showed that this benefit was not apparent in patients with baseline proteinuria of <0.5 g/day [11]. A critical analysis of the AIPRD reports identified several worrisome potential drawbacks in the meta-analyses. First, 2 of the 11 studies were unpublished personal communications. Second, the average age of the 1,860 pooled cohort is 52 years (range 46–63), with a mean duration of only 2.2 years (range 0.9–2.4), and generally, these studies utilized lower end doses of the various ACEIs. Furthermore, very significant scientific extrapolations were made by the AIPRD Study Group with respect to the degree of proteinuria in relation to renal outcomes and response to ACE inhibition. To our surprise, the methods and frequencies of measurement of proteinuria in the pooled 11 randomized clinical trials (RCTs) were disparate – 10 studies reported urine protein excretion as total 24-hour urine protein excretion, whereas 1 study performed dipstick urinalysis on untimed urine samples with results noted as either 'positive' or 'negative'. Besides, remarkably, there was no standardization of the protocol for BP

measurements in the 11 pooled RCTs. BP was measured using a mercury sphygmomanometer in 9 trials and a calibrated automatic device in 2 others. Systolic and diastolic BPs were measured after 5–10 min of rest in the supine position in 10 trials, and in the sitting position in 1 trial. We will submit that, given the limitations of BP measurement in general with its inherent variability and lability [14], and cognizant of the different BP measurement protocols, strong deductions cannot be justifiably made on BP data analysis. Finally, all 1,860 patients were nondiabetics, and the extrapolation of such prognostication to diabetic CKD patients may be unscientific.

Additionally, Griffin and Bidani [14] recently published a critical review of the basic science and clinical science evidence base for the renoprotective specificity of renin-angiotensin system (RAS) blockade. They concluded that a critical review of the available scientific evidence suggests that the specificity of renoprotection that is provided by RAS blockade has been greatly overemphasized [14]. They affirmed that little evidence of truly BP-independent renoprotection was observed in experimental animal models only when ambient BP was assessed adequately by chronic continuous BP radiotelemetry [14]. They went further to state that even when interpreted favorably, the absolute magnitude of the BP-independent component of the renoprotection that is observed with RAS blockade is much smaller than what is due to its antihypertensive effects [14].

We must acknowledge that the factors that contribute to this epidemic of ARF/CKD/ESRD in the USA are not fully understood and must be multifactorial [3–5, 7]. In recent years, some reports have raised concerns about the nonavailability of robust data regarding adverse effects of these agents, more so given the fact that many RAAS blockade trials have often utilized lower doses of these agents, in selected, usually younger, patients, and often for a relatively short duration [15–17]. Also, the over-reliance of this evidence base on a combination of so-called surrogate renal endpoints, without obvious mortality benefits, raises further doubt about the claims of superiority of renoprotection with the ACEIs and ARBs [15–17]. Even more perplexing have been the published meta-analysis-based data contending the validity of claims of superiority of ACEIs and ARBs for renoprotection beyond BP lowering [8]. Indeed, Svensson et al. [18], in a post-hoc analysis of the micro-HOPE (Heart Outcomes Prevention Evaluation) trial patients, demonstrated unequivocally that the patients who received ramipril had a much lower BP reduction as measured by 24-hour ambulatory BP monitoring. The findings of Svensson et al. [18] lend support to the proponents of the arguments that office BP measurements which form the basis of many RCTs have significant limitations with inherent variability and lability [14], and that in clinical trials, scientific extrapolations based on BP data alone must indeed be made with some caution. The recent disappointing results of combination ACEI + ARB therapy in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) report adds more fuel to the ongoing controversy over the adequacy of claims of renoprotection with ACEI/ARB therapy [19].

The association of ARF exacerbation in CKD patients, concurrently on ACEI or ARB, is well reported and acknowledged in the medical literature and has often incriminated associations with well-defined and known so-called precipitating risk factors [15–17]. However, most of these reports are retrospective reviews, small case series and case reports [15–17]. Also, common reversibility of renal failure after discontinuation of the RAAS blockade is implied in these reports, with only a few cases of ESRD having been reported [15–17].

Based on this author's earlier anecdotal experiences in various clinical practice settings in the Baltimore, Md., area between 1996 and 2002, we had speculated that the extent and spectrum of iatrogenic renal failure associated with the use of ACEIs and/or ARBs remained underdiagnosed and unrecognized. Mostly in 2008, we had published several reports of a previously unreported syndrome of late-onset renal failure from angiotensin blockade (LORFFAB), following a 100-patient cohort at the Hypertension Clinic, Midelfort Clinic, Eau Claire, Wisc., USA [15–17, 20]. From our experience, renal failure, sometimes reversible, sometimes progressing to ESRD with resultant increased patient mortality, was usually experienced by older (>65 years) CKD patients on concurrent ACEI/ARB therapy [15–17, 20]. It must be acknowledged that this ARF exacerbation of CKD sometimes occurred in association with previously acknowledged identifiable precipitating factors such as iodinated contrast exposure, acute illness, cardiac surgery and exposure to nonsteroidal anti-inflammatory drugs [15–17, 20]. But even as important, we were able to demonstrate the occurrence of renal failure exacerbation of CKD in patients on ACEI/ARB despite the absence of any identifiable risk factors, the so-called classic LORFFAB situation [15]. Furthermore, we broke a previous myth by demonstrating ARF in CKD in patients on ACEI/ARB with unilateral renal artery stenosis lesions despite functional dual kidneys and often with no other additional precipitating factors present [20].

Table 2. Chronological list of publications associating ARF with concurrent RAAS blockade

Authors	Journal/year	Study type	Study size, n	Clinical scenario	Implicated ACEI/ARB
From et al. [27]	Mayo Clin Proc 2008	retrospective case-matched cohort study	809	contrast-induced nephropathy	ACEI/ARB
Al-Azzam et al. [28]	Ren Fail 2008	prospective cohort study	111	ARF in hospitalized Jordanian patients	ACEI/RB
Khurana et al. [29]	Arch Intern Med 2008	retrospective study	286	ARF after oral phosphate sodium for bowel preparation	ACEI/ARB
Arora et al. [30]	Clin J Am Soc Nephrol 2008	retrospective cohort study	1,386	ARF following cardiac surgery	ACEI/ARB
Onuigbo and Onuigbo [15]	Int Urol Nephrol 2008	prospective longitudinal cohort study	100	general	ACEI/ARB
Onuigbo and Onuigbo [31]	Ren Fail 2008	prospective longitudinal cohort study	7	contrast-induced nephropathy in patients concurrently on RAAS blockade	ACEI/ARB
Onuigbo and Onuigbo [22]	Ren Fail 2008	prospective longitudinal cohort study	5	ARF in CKD in patients on RAAS blockade without precipitating factors	ACEI/ARB
Onuigbo and Onuigbo [32]	QJM 2008	prospective longitudinal cohort study	26	ARF in older CKD patients with renal artery stenosis on RAAS blockade	ACEI/ARB
Onuigbo and Onuigbo [20]	Ren Fail 2008	prospective longitudinal cohort study	26	ARF in older CKD patients with renal artery stenosis on RAAS blockade	ACEI/ARB
Russmann et al. [33]	Am J Gastroenterol 2007	retrospective cohort study	2,352	ARF after oral phosphate sodium for bowel preparation	ACEI/ARB
Komenda et al. [34]	Clin Exp Nephrol 2007	prospective case series	31	contrast-induced nephropathy following cardiac and peripheral angiography	ACEI/ARB
Cirit et al. [35]	Nephron Clin Pract2006	prospective controlled study	230	contrast-induced nephropathy after coronary angiography	ACEI
Toprak et al. [36]	Anadolu Kardiyol Derg 2003	prospective controlled study	80	contrast-induced nephropathy after coronary angiography	captopril
Louis et al. [37]	Ren Fail 1996	prospective cohort study	214	contrast-induced nephropathy	ACEI

More recently, we have reviewed the literature and were able to identify, apart from our own published reports, an increasing number of reports over the last decade, which have identified concurrent use of ACEI/ARB as a risk factor for ARF exacerbations under very different clinical scenarios (table 2). These clinical scenarios include contrast-induced nephropathy, after cardiac surgery, and following the use of oral phosphate sodium preparations for lower bowel preparations (table 2).

From the foregoing, we conclude that regardless of the strength, veracity and rigor of the evidence base for some plausible renoprotection with ACEI/ARB, it must be borne in mind by the practicing physician that the potential for iatrogenic renal failure with these agents cannot be overemphasized. Despite the lower BP together with the higher reduction in proteinuria achieved among the 8,502 patients in the combination arm of ramipril + telmisartan in the just released ONTARGET study, more patients in this combination arm experienced higher rates of dialysis, greater rates of doubling of serum creatinine and even increased mortality rates [19] (table 1). There is the contention that a too low dose of the ACEI was used. Some arguments against the study have raised concerns about incomplete data analysis, especially with reference to the frequency of testing for proteinuria. However, the large size of the study and the long follow-up are very strong points in support of the findings of the ONTARGET study [19]. Furthermore, we cannot agree more with the principal investigators of ONTARGET who recently concluded in a subsequent publication in

the *Lancet* that proteinuria reduction by itself cannot be taken as a definitive marker of improved renal function [21]. They further opined that the benefits of any treatment, including combination RAAS blockade on major renal outcomes, remain to be demonstrated [21]. We submit that the results of the ONTARGET trial support the conclusion that until more studies are available, the use of combination ACEI + ARB should be the exception, rather than the rule.

Despite little supportive evidence in the literature regarding the DOQI (Disease Outcomes Quality Initiative) guidelines in the use of ACEIs and ARBs in CKD patients with proteinuria <0.5 g/24 h, we hold the supposition that since they may be renoprotective, these agents should be initiated as recommended under current guidelines. However, providers must be cognizant of the limited evidence base for their use in these indications and should therefore be amenable to discontinuing them when indicated by new-onset unexplained loss of estimated GFR at any point in time. We agree with current guidelines that at drug initiation of treatment with an ACEI, an ARB or a combination of both, an initial rise of <30% above baseline serum creatinine should not call for drug discontinuation. However, this rise in serum creatinine must be limited in time and scope and must be nonprogressive. We note that data from our 100-patient cohort showed that many of them experienced the >25% increase in baseline creatinine, as measured in the preceding 3 months, even after years on the same dose of the RAAS blocking agent. Fifty-one patients were on the same agent and same dose for more than 12 months at enrollment when they experienced worsening renal failure [15–17, 20]. With the acknowledgement that most of the renoprotection literature with ACEIs and ARBs derived from studies of relatively younger patients (<60 years), and cognizant of the relatively short duration of many of the trials, and given the fact that many trials often utilized lower end doses of the various agents, we have recommended that in older patients (>65 years), there is the overriding need to 'start low and go slow' with drug dose escalation with RAAS blocking agents [22]. The overarching need to protect the kidneys in our CKD patients mandates close and indefinite monitoring of serum creatinine and estimated GFR in these patients, and the treating physician must be ready to discontinue ACEI/ARB if there is confirmed progressive and continuous loss of kidney function, after all other potential causes have been excluded by standard nephrology work-up. What is more, from our 1-center experience [15–17, 20], 'renoprevention', a term we have coined to cover the temporary pre-emptive withdrawal of ACEI/ARB, before iodinated contrast administration, during any acute illness, prior to elective cardiac surgery, perioperatively for all major surgical operations, and before oral phosphate sodium ingestion, more so in older (>65 year) CKD patients, will only further improve the results of renoprotection with ACEI/ARB therapy [15–17, 20].

Finally, we submit that the increasing numbers of ARF, CKD and ESRD patients being recognized in the USA and worldwide represent an epidemic. We agree that the cause(s) of these epidemics remain unclear, poorly elucidated and must be multifactorial. All we are trying to do is to draw attention to the plausible contribution, in whatever magnitude, of the use of the ACEIs and ARBs in the possible propagation of these epidemics. Increased provider awareness of this potential is necessary, and clearly, more research is needed.

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Editorial Comment

M. El Nahas, Sheffield

The review by Onuigbo raises issues relating to the increasingly indiscriminate use of inhibitors of the RAS in patients with CKD. Most national and international guidelines recommend the use of ACEIs or ARBs in the majority of patients with CKD. For instance, the recent (2008) UK NICE (National Institute for Health and Clinical Excellence) CKD guidelines recommend the use of ACEI/ARB in hypertensive patients with nondiabetic CKD who have a proteinuria >0.5 g/24 h, and even in those who are normotensive and whose proteinuria exceeds 1 g/24 h. These recommendations are based on experimental evidence of benefit in a number of models of CKD in rodents and on data derived from studies of diabetic nephropathy and proteinuric CKD in humans. Whilst the experimental evidence of benefit of these agents is strong, the clinical evidence in nondiabetic CKD is much weaker, if not nonexistent. In fact, there is not a single valid randomized control trial of these agents in nonproteinuric (<1 g/24 h), nondiabetic CKD patients. The strongest evidence derives from the REIN (Ramipril Efficacy in Nephropathy) trial of ramipril in heavily proteinuric CKD patients. Indirect evidence derives from meta-analyses of original studies and pooled data where a beneficial effect is not invariably independent from a blood pressure-lowering effect. The minireview highlights many of these shortcomings. It also raises concern about the impact of inhibition of RAS on kidney function in susceptible individuals where it can precipitate severe renal insufficiency. Acute kidney disease or CKD is increasingly recognized as a common cause of progressive CKD, especially in the elderly, and awareness of the potential nephrotoxicity of these agents in this age group is of paramount importance. Further, the review also draws attention to the recent concern of the potential nephrotoxicity of combination therapy with ACEI and ARB in susceptible individuals. A critical re-evaluation of the risk/benefit of inhibition of the RAS in CKD is necessary.