Should We STOP Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers in Advanced Kidney Disease?

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\section*{Introduction}

Chronic kidney disease (CKD) is a worldwide public health problem associated with a high prevalence of cardiovascular disease (CVD) and impaired quality of life [1, 2]. Kidney disease has the lowest evidence base for clinical interventions of any specialist area of clinical medicine [3]. Interventions to delay the progression of renal disease are limited. The focus of previous research has been blood pressure (BP) reduction and limiting proteinuria. High-quality research in renal medicine has improved recently with the publication of several well-designed, randomised controlled trials (RCTs) including SHARP, EVOLVE and BEACON [4–6]. Unfortunately, several of these produced predominantly negative findings but were of clinical importance to direct future clinical practice and research.

Angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor antagonists (ARB) are commonly used in patients with early CKD, but their value in advanced CKD (estimated GFR (eGFR) ≤30 ml/min/1.73 m\textsuperscript{2}) is unknown. There remains a debate about the omission of ACEi/ARB in patients with advanced CKD and their use in association with CVD or heart failure. Does the potential gain in eGFR with ACEi/ARB cessation outweigh the potential adverse cardiovascular outcomes? This paper reviews the current literature that addresses this issue. Several controversies are discussed. Although lowering BP reduces cardiovascular events, evidence suggests that ACEi/ARBs are not superior to other antihypertensive agents. There are no studies assessing the benefits of ACEi/ARB therapy in cardiovascular risk reduction in advanced non-dialysis CKD. The STOP ACEi trial will strengthen the evidence base and shed light on the potential merits and dangers of ACEi/ARB use in advanced CKD on renal function and cardiovascular outcomes.

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shown variable effects on cardiovascular events with use of ACEi [17, 18], while the rate of decline of renal function remains a strong predictor of mortality [19–22].

Uncertainty in the Use of ACEi/ARBs in Advanced CKD

There are differing opinions about the omission of ACEi/ARB in patients with advanced CKD and their use in association with CVD or heart failure (HF). Does the potential gain of eGFR with ACEi/ARB cessation lead to improved morbidity and mortality or an increase in adverse cardiovascular outcomes? Recent cardiovascular guidelines have recommended caution with the use of ACEi/ARBs for patients with HF and advanced CKD [23]. The potential merits and risks of ACEi/ARB use in advanced CKD is in a state of equipoise and has formed the basis for the current UK-based STOP-ACEi trial, a randomised controlled open label study of ACEi/ARB withdrawal in progressive and advanced CKD [24]. The results of this trial could be critical to delaying the need for expensive and invasive dialysis therapy without being a detriment to other outcomes such as cardiovascular events [25].

CVD is a leading cause of death in patients with advanced kidney disease. Data from the UK Renal Registry suggest an overall incident death rate for patients commencing dialysis of 261 per 1,000 patient years. CVD, infections and dialysis withdrawal account for most of these deaths (27, 21 and 16%, respectively) [26]. There are similar data from the USRDS with an adjusted mortality rate for haemodialysis of 172 per 1,000 patient years, which increases to 400 in the first 2 months after commencing haemodialysis [27]. CVD accounted for 41% of all deaths. Kidney transplantation is associated with better clinical outcomes and quality of life but remains a scarce commodity and is not an option for many dialysis patients in whom associated co-morbidity precludes transplantation [19]. In this population, dialysis avoidance has to be balanced against cardiovascular risk. STOP ACEi aims to address the gaps in knowledge and consider the potential merits and risks of ACEi/ARB use in advanced CKD on renal function, delaying the start of dialysis and cardiovascular outcomes.

Why Use ACEi/ARBs in Earlier Stages of CKD?

Advanced CKD (stage 4–5), is associated with an increased relative risk (RR) of death of around 2.5-fold and a RR of kidney failure, as defined by a requirement for renal replacement therapy (RRT) of up to 50-fold compared to that of age-matched individuals with ‘normal’ kidney function [28–32]. Matsushita et al. confirmed that both CKD and albumin:creatinine ratio (ACR) predict all cause and CVD mortality in the general population [33]. Their meta-analysis, in which they examined 105,872 participants with over 730,577 person-years of data found a linear relationship of eGFR and albuminuria with cardiovascular death [33]. This was in patients with CKD stage 4 or better. The presence of CKD has a major negative impact on a range of other outcomes including quality of life [19, 25] and is a predictor of increased cardiovascular mortality in CKD [34].

In a study from Taiwan, Wen et al. examined a cohort of 462,293 individuals aged over 20, in which the prevalence of CKD was 11.9% (95% CI 11.7–12.3) [35]. Those with CKD had an 83% higher all-cause mortality (hazard ratio, HR 1.83; 95% CI 1.73–1.93). Mortality was 100% higher for CVD (HR 2.00; 95% CI 1.78–2.25). The median follow-up for this cohort was 7.5 years. In the entire population, 10.3% (95% CI 9.57–11.03) of deaths were attributable to CKD.

ACEi/ARBs have demonstrated a cardio-protective effect in the non-CKD population. They lower morbidity and mortality in patients with HF (CHARM) and reduce cardiovascular events in high-risk patients (HOPE) [36, 37]. Close examination of the HF studies provides little information to direct care in advanced CKD as patients with significant renal dysfunction were excluded (table 1) [36–46]. The HOPE study showed that ramipril did not significantly reduce office BP (8/2 mm Hg, p = NS) or daytime ambulatory BP (6/2 mm Hg, p = NS) after 1 year, but 24-hour ambulatory BP was significantly reduced (10/4 mm Hg, p = 0.03). This was mainly because of a more pronounced BP-lowering effect during night-time (17/8 mm Hg, p < 0.001). The effects on cardiovascular morbidity and mortality seen with ramipril in the HOPE trial appear to relate to effects on BP over a 24-hour period [47].

ALLHAT and other studies (table 2) [7, 9–11, 36, 48–53] have shown suppression of the renin angiotensin aldosterone system (RAAS) to be effective in slowing the progression of kidney disease in patients with CKD stage 3 or better. The benefit of ACEi and ARB cannot be solely attributed to BP reduction in patients with proteinuria. Angiotensin II suppression results in vaso-relaxation, preferentially of the efferent arteriole in the glomerulus leading to reduced intraglomerular pressure and a significant antiproteinuric effect [10]. The mechanisms through which albuminuria reduction delays renal disease progression may be via altered glomerular permeability to macromol-
molecules, which negates the subsequent large protein exposure to both the podocytes and tubular cells that would otherwise lead to progressive glomerulosclerosis and loss of GFR. Increased glomerular filtration of albumin and other macromolecules increases the requirement of albumin reuptake in proximal tubular cells. This results in a signalling cascade promoting release of vasoactive, inflammatory, and fibrotic substances and eventual tubulointerstitial damage and functional deterioration.

**Why Use STOP ACEi/ARBs in Advanced CKD?**

Patients with advanced CKD have a high burden of CVD and potentially stand to gain from the cardio-protective effect of RAAS antagonism. Other factors outside of RAAS activation such as CKD-mineral bone disease, FGF-23 and association with left ventricular hypertrophy [54], inflammation and oxidative stress may account for the majority of the exponential increase of cardiovascular events associated with advanced CKD [55]. ACEi/ARB cessation theoretically restores the capacity for auto-regulation within the kidney, allowing RAAS activation and results in a rise in the GFR. In advanced CKD, even a modest increase in GFR could delay the onset of RRT. ACEi/ARB cessation could also prevent episodes of acute kidney injury in advanced CKD caused by intercurrent illness and infections. These episodes are often the tipping point and lead to the initiation of long-term dialysis therapy. This is especially true of high-risk populations such as the elderly and patients with HF [56]. It is imperative to bal-

<table>
<thead>
<tr>
<th>Trial (reference)</th>
<th>Intervention</th>
<th>Cohort</th>
<th>Sample</th>
<th>Follow-up</th>
<th>Creatinine/ eGFR</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS [46]</td>
<td>Enalapril vs. placebo</td>
<td>NYHA IV HF</td>
<td>253</td>
<td>188 days</td>
<td>124–132 μmol/l</td>
<td>Improved symptoms and life expectancy vs. placebo, no impact on sudden cardiac death</td>
</tr>
<tr>
<td>Val-HeFT [43]</td>
<td>Valsartan vs. placebo</td>
<td>NYHA I–II HF</td>
<td>5,010</td>
<td>27 months</td>
<td>58 ml/min</td>
<td>Reduced composite mortality and morbidity and improved symptoms</td>
</tr>
<tr>
<td>V-HeFT-II [45]</td>
<td>Enalapril vs. hydralazine/ isosorbide dinitrate</td>
<td>Men; NYHA class II–III HF</td>
<td>804</td>
<td>2.5 years</td>
<td>Not measured</td>
<td>Sudden death 14%; mortality from progressive HF 12 vs. 23%</td>
</tr>
<tr>
<td>SOLVD-treatment [44]</td>
<td>Enalapril vs. placebo</td>
<td>NYHA class II/III HF and EF &lt;35%</td>
<td>2,569</td>
<td>41 months</td>
<td>1.2 mg/dl (106 μmol/l)</td>
<td>Sixteen percent fewer deaths in enalapril group (p = 0.0036), 26% less hospitalizations (p &lt; 0.0001)</td>
</tr>
<tr>
<td>SOLVD-prevention [42]</td>
<td>Enalapril vs. placebo</td>
<td>Asymptomatic patients with EF ≤35%</td>
<td>4,228</td>
<td>37 months</td>
<td>1.2 mg/dl (106 μmol/l)</td>
<td>Eight percent lower mortality (NS); fewer deaths and hospitalizations due to HF (p &lt; 0.001)</td>
</tr>
<tr>
<td>CHARM-added trial [38]</td>
<td>Candesartan vs. placebo</td>
<td>LV dysfunction already taking ACEi</td>
<td>2,548</td>
<td>42 months</td>
<td>Not measured excluded &gt;3.0 mg/dl (265 μmol/l)</td>
<td>Candesartan significantly improved all-cause mortality</td>
</tr>
<tr>
<td>CHARM alternative [37]</td>
<td>Candesartan vs. placebo</td>
<td>LV dysfunction intolerant to ACEi</td>
<td>2,028</td>
<td>42 months</td>
<td>Nil Excluded &gt;3.0 mg/dl (265 μmol/l)</td>
<td>Candesartan significantly improved all-cause mortality</td>
</tr>
<tr>
<td>ELITE I [39]</td>
<td>Losartan vs. captopril</td>
<td>&gt;65 years with HF NYHA II–IV; EF &lt;40%</td>
<td>722</td>
<td>48 weeks</td>
<td>106 μmol/l</td>
<td>No difference in outcomes of worsening renal function</td>
</tr>
<tr>
<td>ELITE II [40]</td>
<td>Losartan vs. captopril</td>
<td>&gt;60 years with HF NYHA II–IV; EF &lt;40%</td>
<td>3,152</td>
<td>555 days</td>
<td>Nil</td>
<td>No difference in all-cause mortality 1.13 (0.95–1.35)</td>
</tr>
<tr>
<td>ATLAS [41]</td>
<td>Lisinopril vs. losartan</td>
<td>LV dysfunction</td>
<td>3,163</td>
<td>~4 years</td>
<td>1.3 mg/dl (117 μmol/l)</td>
<td>Reduced mortality 8% NS Combined death and hospitalisation 15%</td>
</tr>
</tbody>
</table>

**EF = Ejection fraction; NYHA = New York Heart Association.**

ACEi/ARB in Advanced Kidney Disease

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ance the potential benefits of ACEi/ARB therapy in advanced CKD with their potential to accelerate the need for RRT.

### What Happens to Individuals with CKD and Proteinuria?

A recent analysis of 141,413 US veterans (mean age 75 ± 10; 22% with diabetes) assessed the association between ACEi/ARB use and all-cause mortality in patients with known non-dialysis requiring CKD (GFR >60 ml/min + proteinuria vs. GFR <60 ml/min) [57]. The authors found that the use of ACEi/ARBs declined as the eGFR declined; for a 10 ml/min higher eGFR the likelihood of ACEi/ARB prescription rose by 13% (OR 1.13; 95% CI 1.12–1.15; p < 0.01) [57]. Comparison of the 2 groups showed that between those taking vs. not taking an ACEi/ARB, there was a significant benefit of ACEi/ARB use with a mortality reduction both in the intention-to-treat (ITT) analysis (HR 0.81; 95% CI 0.78–0.84; p < 0.001) and the as-treated (AT) analysis with inverse probability of treatment (OR 0.37; 95% CI 0.34–0.41; p < 0.001). Few patients in this cohort had advanced CKD (approximately 6% had an eGFR of <30 ml/min/1.73 m²) [57]. The current body of evidence is insufficient to guide the use of ACEi/ARBs in patients with advanced CKD. Adequately powered randomised control trials to elucidate a potential benefit from cessation of ACEi/ARBs in patients with advanced CKD would be of enormous value to guide optimal clinical practice and delay renal progression and the need for RRT. This has formed the basis for the STOP ACEi trial [24], but should this apply to all high-risk groups?

### Table 2. Average GFR/serum creatinine at baseline entry into trials

<table>
<thead>
<tr>
<th>Trial (reference)</th>
<th>Intervention</th>
<th>Cohort</th>
<th>Sample</th>
<th>Follow-up, years</th>
<th>Baseline creatinine (median)/eGFR</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDNT [7]</td>
<td>Irbesartan vs. amlodipine vs. placebo</td>
<td>DMII with nephropathy</td>
<td>1,713</td>
<td>3</td>
<td>59 (47) μmol/l CrCl 56.3 ml/min</td>
<td>Composite of doubling SC; ESRD; death 20 vs. 28%</td>
</tr>
<tr>
<td>RENAAL [11]</td>
<td>Losartan vs. placebo</td>
<td>DM II with nephropathy</td>
<td>1,513</td>
<td>3</td>
<td>58 (40) ml/min 1.9 mg/dl (167 μmol/l)</td>
<td>Composite of doubling SC; ESRD death</td>
</tr>
<tr>
<td>CSG captopril [10]</td>
<td>Captopril vs. placebo</td>
<td>DM I with nephropathy</td>
<td>409</td>
<td>4</td>
<td>68 ml/min</td>
<td>Doubling SC 12.1 vs. 21.3%</td>
</tr>
<tr>
<td>ALLHAT [48]</td>
<td>Lisinopril vs. amlodipine vs. chlorothiazide vs. doxazosin</td>
<td>Hypertension and CVD</td>
<td>33,357</td>
<td>4.9</td>
<td>71–78 ml/min</td>
<td>CV end points NS</td>
</tr>
<tr>
<td>BENEDICT [9]</td>
<td>Trandolapril vs. verapamil</td>
<td>Hypertension DMII</td>
<td>1,204</td>
<td>3.6</td>
<td>79 ml/min 0.8 (79.2)</td>
<td>Reduce or prevent microalbuminuria</td>
</tr>
<tr>
<td>ACCOMPLISH [50]</td>
<td>Benazepril and amlodipine vs. benazepril and thiazide</td>
<td>HT + CVD renal CKD</td>
<td>11,506</td>
<td>3</td>
<td>1.0 mg/dl 78.9 ml/min</td>
<td>CV events 0.8 (0.72–0.9)</td>
</tr>
<tr>
<td>ROADMAP [49]</td>
<td>Olmesartan vs. placebo</td>
<td>DM II</td>
<td>4,447</td>
<td>3.2</td>
<td>77.4 μmol/l (eGFR 85 ml/min)</td>
<td>Microalbuminuria onset; 1% in each group had double SC</td>
</tr>
<tr>
<td>ROAD [51]</td>
<td>ACEi/ARB</td>
<td>IgA nephropathy</td>
<td>360</td>
<td>3.7</td>
<td>2.7 mg/dl (30.6 ml/min)</td>
<td>X2 SC; ESRD and death</td>
</tr>
<tr>
<td>AASK [52]</td>
<td>Ramipril amlodipine metoprolol</td>
<td>African American hypertensive nephrosclerosis</td>
<td>1,089</td>
<td>3.8</td>
<td>198 μmol/l 46.8–48.1 ml/min</td>
<td>Rate of decline in eGFR</td>
</tr>
<tr>
<td>REIN [8]</td>
<td>Ramipril vs. placebo</td>
<td>Non diabetic CKD</td>
<td>352</td>
<td>3</td>
<td>56 ml/min</td>
<td>Decline in GFR</td>
</tr>
<tr>
<td>AIPRI [13]</td>
<td>Benazepril vs. placebo</td>
<td>CKD any cause</td>
<td>583</td>
<td>~3</td>
<td>52 ml/min</td>
<td>Doubling SC or ESRD</td>
</tr>
</tbody>
</table>

Ahmed/Jorna/Bhandari

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Renin-Angiotensin-Aldosterone-System Inhibition in Diabetic Nephropathy

Diabetic nephropathy is associated with low renin levels but a higher level of intrarenal angiotensin II production. The high degree of RAAS activation accounts for the elevated vasodilator effect of ACEi/ARBs in patients with diabetic nephropathy and the significant benefit in reducing proteinuria [58]. Several large trials have examined the relative potential benefits of ACEi/ARB use in patients with diabetes mellitus. Some of these trials included patients with relatively well-preserved renal function at baseline (table 2). The BENEDICT trial demonstrated that trandolapril postponed the onset of microalbuminuria [9]. In the CSG captopril trial, the captopril treated arm had a lower rate of doubling of serum creatinine (SC; 12.1 vs. 21.3%; p = 0.007) [10]. The investigators observed a more pronounced effect in patients whose renal function was worse at baseline but still well preserved at the time of recruitment to the study [10].

The Irbesartan in Diabetic Nephropathy Trial (IDNT) showed that treatment with Irbesartan was associated with a reduction in the primary composite outcome of doubling of SC, development of end-stage renal disease (ESRD) and death by 20% in comparison with the placebo group and 23% in comparison with the amiodipine group [7]. The effect was independent of a difference in BP across the groups. IDNT included patients with SC between 1.0 and 3.0 mg/dl [7].

The RENAAL study in 2001 demonstrated that Losartan significantly reduced the incidence of a composite outcome of doubling of the baseline SC, development of ESRD or death [11]. The degree of proteinuria at baseline and 6 months after therapy were strong predictors of renal outcome suggesting that the anti-proteinuric action of ACEi/ARBs was largely responsible for their renoprotective effect. Losartan had no effect on the rate of death or the composite outcome of morbidity and mortality from cardiovascular causes, which was similar to placebo [11, 12]. Post hoc analysis of the RENAAL study separated the study group into 3 tertiles according to their baseline SC. There was a decrease in the risk of ESRD by 24.6, 26.3 and 35.5%, respectively in the highest (2.1–3.6 mg/dl), middle (1.6–2.0 mg/dl) and lowest (0.9–1.6 mg/dl) tertiles. The result suggests that the renoprotective effect of RAAS blockade may extend to patients with an SC >2.0 mg/dl (176 μmol/l) [59].

In 2006, a Cochrane review explored the use of ACEi/ARBs in preventing the progression of kidney disease in a diabetic patient population. The review included 49 studies with 12,067 diabetic patients at all stages of kidney disease. It included studies that compared ACEi or ARB to placebo and studies that directly compared ACEi and ARB. The authors found that both ACEi and ARB improved renal outcomes (ESRD, doubling of SC, prevention of progression and remission from micro- to macroalbuminuria) [60]. When compared to placebo, the use of ACEi at maximum tolerated doses appeared to prevent death in patients with diabetic nephropathy (RR 0.78; 95% CI 0.61–0.98). This mortality benefit was not found with ARB. The authors suggested that the beneficial effect seen in terms of the loss of GRF was perhaps due to their known anti-proteinuric effects; however, there was a paucity of high-quality evidence to state benefit in advanced CKD and the conclusions were based mainly on composite end points [60]. A recent systematic review and meta-analysis of patients with diabetes (largely without microalbuminuria or proteinuria) with 95,910 patient-years of follow-up from randomized trials did not find evidence of superiority of RAAS blockade over other antihypertensive medications to reduce cardiovascular and renal outcomes [61].

Evidence suggests that for diabetic nephropathy, RAAS suppression limits the onset of proteinuria, reduces proteinuria in established nephropathy and improves the composite outcomes and death and loss of GFR independent of a BP-lowering effect. The reduction in the rate of decline in renal function was independent of baseline renal function; however, patients with advanced CKD were excluded from these studies. It may be that ACEi/ARB use in advanced CKD leads to loss of the adaptive response to maintain renal perfusion and protect the kidneys during this critical phase.

How Useful Is Reducing Proteinuria to Slow the Rate of Decline of GFR?

The ROADMAP study showed that olmesartan was associated with a delayed onset of microalbuminuria in patients with type 2 diabetes with normal kidney function and no albuminuria compared to placebo, even though BP control in both groups was comparable. Olmesartan was associated with a significant reduction in eGFR (about 4 ml/min/1.73 m²) [49]. There was concern over the higher rate of fatal cardiovascular events with olmesartan among patients with pre-existing coronary heart disease. The drop in eGFR and the lower rate of microalbuminuria in the olmesartan group could represent a haemodynamic (functional) response to lower glomerular pressure or an underlying structural change [49].
Authors of ROADMAP and those from ALTITUDE and ACCOMPLISH suggest that microalbuminuria is a poor surrogate for renal outcomes [50, 62]. Although most of the studies tested drugs that intervened in RAAS, the strength of the association between reductions in albuminuria and ESRD was not different with other interventions that decreased albuminuria. Few studies have prospectively assessed whether targeting of albuminuria delays progression of renal disease. The Renoprotection of Optimal Antiproteinuric Doses trial in patients with IgA nephropathy demonstrated that a regimen with either an ACEi or an ARB targeted to achieve a maximal anti-albuminuria response is associated with marked improvement in renal survival compared with a fixed maximal antihypertensive dose of these agents [49].

In the post hoc analysis of the IDNT, Irbesartan safely and significantly slowed the rate of change in eGFR (–2.34 ml/min/1.73 m²/year) compared to amlodipine (–3.76 ml/min/1.73 m²/year) and placebo (–3.52 ml/min/1.73 m²/year) at similar BP control and conferred renoprotection in patients with diabetic nephropathy (average eGFR 46.4 ml/min/1.73 m²) [7].

A follow-up study with pre-specified secondary outcomes from the ALTITUDE data in patients with type II diabetes mellitus demonstrated that treatment delayed progression of microalbuminuria to macroalbuminuria (HR 0.83; 95% CI 0.75–0.93) and improved regression of albuminuria (HR 1.29; 95% CI 1.19–1.39) [63]. It found no benefit in CKD progression (‘hard renal outcomes’) neither in the overall population nor in the sub-groups. This confirmed the questionable use of microalbuminuria as a surrogate marker for renal outcomes. A recent meta-analysis from Heerspink et al confirmed that there is still controversy with the use of surrogate end points such as proteinuria and this requires further validation in clinical trials [64]. Contrary to this, multiple clinical studies have shown a strong and independent association between albuminuria and ESRD and that initial treatment induced change in albuminuria predicts subsequent renal risk. The correlation analyses from RCTs between changes in albuminuria and ESRD were conducted post hoc and were no longer based on randomized comparisons raising the possibility that the lower risk of ESRD among patients with a reduction in albuminuria was caused by factors unrelated to this [64].

A recent meta-analysis of 23 trials including patients with both type 1 and 2 diabetes mellitus compared ACEi with placebo or active drugs (32,827 patients) and 13 trials compared ARBs with placebo (23,867 patients). The use of ACEi showed a significant reduction in all-cause mortality of 13%. Of these, cardiovascular deaths were reduced by 17% and major cardiovascular events by 14%, including myocardial infarction by 21% and HF by 19%. Treatment with ARB did not show significant effect on all-cause mortality, cardiovascular death rate or major cardiovascular events with the exception of HF [65]. Neither ACEi nor ARB was associated with a decrease in the risk of stroke in patients with diabetes mellitus. Many trials in that meta-analysis did not have information about kidney function and others included CKD stage 3. The primary outcome was all-cause mortality and cardiovascular deaths but not progression of kidney disease. ACEi and ARB were compared indirectly with different dosages and there was variation in diabetic and BP control between the studied populations. The trials of ACEi and ARB were not comparable in size [65].

The telmisartan randomised assessment study in ACEi-intolerant subjects with CVD demonstrated a greater decline both in eGFR and in the incidence of doubling of SC with telmisartan (HR 1.59; 95% CI 1.04–2.41) [66].

**Renin-Angiotensin-Aldosterone-System Inhibition in Non-Diabetic Renal Disease**

Maschio et al. [13] demonstrated that benazepril protected against the progression of CKD despite an average increase of 0.2 mg/dl (17.6 μmol/l) in SC in the group receiving ACEi during the first month. The study population had mild to moderate CKD at baseline with renal disease of various aetiologies including diabetic nephropathy. The improvement in renal outcomes was greater in those with glomerular diseases, diabetic nephropathy and urinary protein excretion >1 g per 24 h. The overall mortality rate in the benazepril group was 1 death per 93 patient-years, which was higher than the rate in the placebo group (1 per 656 patient-years). It was not clear why there were more deaths in the benazepril group than in the placebo group [13].

Hou et al. [14] recruited 422 non-diabetic CKD patients in a randomised, double blind study to observe the effect of benazepril vs. placebo. The patients were divided into 2 groups based on their renal function; Group 1 had a SC 1.5–3.0 mg/dl and Group 2 a SC 3.1–5.0 mg/dl. Only Group 2 patients were assigned to the placebo arm as the ethics committee felt the Group 1 patients should not be given placebo because of the growing evidence of a renoprotective effect of ACE inhibition in patients with earlier stages of CKD. Over a 3.4-year follow-up period, the
investigators observed a significant reduction in the primary outcome, a composite of a doubling of the SC, ESRD or death, in the benazepril arm of Group 2. The calculated GFR in Group 2 patients assigned to benazepril was 26.3 ± 5.3 ml/min/1.73 m². There are, however, doubts about the validity of this study, including a duplicate publication using the same study groups but with different and conflicting data [14, 67].

The REIN study showed a significant reduction in the rate of GFR decline in patients with non-diabetic CKD and proteinuria treated with ramipril vs. conventional therapy above and beyond what was expected with the degree of reduction in BP [68]. The decline in GFR was inversely correlated with the reduction in proteinuria. All patients had proteinuria >1 g/day at baseline. Assessment of the published data from the REIN study indicated a limited effect of ACE inhibition on CKD progression despite a large difference in composite end points including doubling of SC [69]. The REIN-2 study in non-diabetic CKD patients randomised to ramipril 2.5–5 mg (standard, n = 168) vs. ramipril 5–10 mg and felodipine 5–10 mg (intensive, n = 167) found a significant reduction in BP but no significant difference in CKD progression [70]. Post-hoc analysis of 322 patients (Ruggenenti et al. [69]) suggested that therapy should be offered to all patients with CKD, even those with a GFR between 10 and 30 ml/min/1.73 m². The decline in GFR was inversely correlated with the reduction in proteinuria. All patients had proteinuria >1 g/day at baseline. Assessment of the published data from the REIN study indicated a limited effect of ACE inhibition on CKD progression despite a large difference in composite end points including doubling of SC [69]. The REIN-2 study in non-diabetic CKD patients randomised to ramipril 2.5–5 mg (standard, n = 168) vs. ramipril 5–10 mg and felodipine 5–10 mg (intensive, n = 167) found a significant reduction in BP but no significant difference in CKD progression [70]. Post-hoc analysis of 322 patients (Ruggenenti et al. [69]) suggested that therapy should be offered to all patients with CKD, even those with a GFR between 10 and 30 ml/min/1.73 m². In this seminal study, there was no nephro-protection effect when baseline proteinuria was <1.5 g/24 h suggesting that the beneficial effects of ACEi may be limited to those with ‘pure’ glomerular disease rather than those with low level proteinuria and who may have ischaemic CKD.

The current evidence supports the use of RAAS blockade in proteinuric non-diabetic renal disease (>1 g/24 h). In the REIN cohort, hypertension and proteinuria predicted decline in renal function, while the baseline renal function did not. Notably, a few patients with severe renal impairment were included at baseline. The renal-protection benefit of ACEi/ARBs in patients without proteinuria beyond an antihypertensive effect has not been demonstrated.

Is More RAAS Inhibition Better? – Adverse Outcomes in Dual Blockade

Several therapeutic options to inhibit the renin-angiotensin-aldosterone system have been developed including ACEi, ARB, aldosterone antagonists and direct renin inhibitors. It had been postulated that dual inhibition may provide additional renal protection based on the theoretical beneficial effects on intra-glomerular pressure and the anti-proteinuric effects.

A meta-analysis of 49 trials comparing monotherapy and dual ACEi/ARB therapy vs. placebo or other agents demonstrated that both ACEi and ARB reduce proteinuria to a similar degree. Combination therapy was more effective than either agent alone, but there were concerns of an increase in adverse effects with the combination therapy (table 1) [71].

ONTARGET explored whether a combination of telmisartan and lisinopril was more effective than each agent alone in preventing cardiovascular events in a population of patients with known vascular disease or diabetes and end-organ damage. After a median follow-up period of 56 months, there was no significant difference in the primary composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for HF among the 3 groups. There was a significant increase in the incidence of acute kidney injury, necessitating dialysis in the combination therapy arm. The participants in this trial had well-preserved renal function with a mean eGFR of 74 ml/min/1.73 m² at baseline and few had significant proteinuria (13% with urine ACR ≥30 mg/mmol). On subgroup analysis of patients with overt diabetic nephropathy, the RR was not significant in the combination group [72].

The safety of dual blockade was further questioned by the outcome ALTITUDE. The study was designed to assess the effects of aliskiren (a renin inhibitor) vs. placebo in combination with either an ACEi or ARB. The trial was stopped early, as the chance of observing a benefit with dual therapy was low and there were an increased number of adverse events in the aliskiren group including non-fatal stroke and hyperkalaemia [62].

Leading on from ONTARGET, VA NEPHRON D tested the use of dual ACEi/ARB therapy in US veterans with type 2 diabetes mellitus and overt proteinuria (a population at high risk of progressive CKD). Patients were commenced on Losartan 100 mg daily and then randomised to receive either lisinopril or placebo. The study was stopped early due to safety concerns. Combination therapy resulted in an increased risk of hyperkalaemia and acute kidney injury. There was no benefit demonstrated with respect to mortality or reduction in cardiovascular events [73].

Finally, in a prospective cohort, the safety and efficacy of combination ACEi/ARB therapy in a study of 28,497 hypertensive adults with advanced CKD (creatinine of >520 μmol/l), it was found that when comparing dual

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ACEi/ARB users (n = 14,117), to non-users (n = 14,380) with a median follow-up of 7 months and using Cox proportional hazards regression models to estimate HR for commencement of long-term dialysis and all-cause mortality. 20,152 patients (70.7%) required long-term dialysis and 5,696 (20%) died before progression to ESRD. The chance of long-term dialysis was reduced by 6% (RR 0.94; 95% CI 0.91–0.97), but hyperkalaemia and hospitalisation rates were higher among ACEi or ARB users. Potential for confounding by indication, that is, the fact that those who had the most need got the drug (clinician bias), is a major limitation of this data set [74].

Are ACEi/ARBs Cardioprotective?

There is an exponential increase in CVD with declining renal function [75]. Despite this there are no studies assessing the benefits of ACEi/ARB therapy on cardiovascular risk reduction in advanced non-dialysis CKD. HF is a complex and difficult area to untangle with limited data. Authors of the SOLVD trial [42, 44] found that older age was associated with a greater risk of loss of GFR, especially in the enalapril group while Hillege et al. showed that GFR reduction was a stronger predictor for mortality than left ventricular ejection fraction or NYHA class [76].

There is no clear evidence for benefit of RAAS blockade for HF in patients with CKD or evidence that discontinuing RAAS inhibitors in patients with advanced CKD (stages 4 and 5) and HF is beneficial or hazardous. This may be due to the complex phenotype of uraemic cardiomyopathy and most of these studies included participants with relatively well-preserved renal function (table 1) [77]; however, it is anticipated that improvement in GFR would reduce the cardiovascular risk burden of these patients. Evidence suggests that the possible improvement in fluid status via improved renal function from ACEi withdrawal may lead to cardiovascular benefits. Furthermore, there have been no studies specific to RAAS inhibition and cardio-protection in advanced CKD and there is little evidence that the cardio-protective benefit of RAAS inhibition is independent of adequate/optimal BP control. Even the HOPE study investigators were unable to provide evidence that cardio-protection (by decreased mortality, myocardial infarction or stroke) by ramipril was independent of improved BP control [47].

It is not known if reduced renal function reduces the beneficial effects of ACEi and other therapies for HF such as beta blockers (table 1). Evidence for therapeutic benefit from blockade of RAAS in chronic HF patients with CKD is lacking, particularly as patients with an SC >221 μmol/l have generally been excluded from therapeutic trials. In a prospective cohort of 6,427 ambulatory patients with ischaemic HF who were treated with ACEi, a significant mortality benefit was seen in patients with a creatinine clearance (CrCl) >60 ml/min but not in patients with a CrCl <60 ml/min [78].

Hsu et al. [74] examined data on patients with newly diagnosed diabetes treated with ACEi or ARB collected from the Taiwan’s National Health Insurance Research Database for the period 2000–2010. A total of 30,777 ARB users and 21,436 ACEi users were identified. One ARB user was matched to one ACEi user by propensity score. ITT and AT models were used. The primary outcomes were myocardial infarction, ischaemic stroke, and all-cause mortality. The secondary outcomes were hospitalization for acute kidney injury and hyperkalemia. Compared with ACEi users (n = 21,436) ARB users (n = 30,777) showed no significant difference in the outcomes of myocardial infarction (HR 0.92; 95% CI 0.80–1.07), ischemic stroke (HR 0.95; 95% CI 0.87–1.04), or all-cause mortality (HR 0.95; 95% CI 0.89–1.01) in the ITT analysis. The risks of hospitalization for acute kidney injury and hyperkalemia did not differ between groups. ACEi and ARB use had similar effects on major adverse cardiac events (MACEs) and adverse effects in the AT analysis. This study supports the comparative effectiveness of ACEi and ARB in terms of MACE outcomes in patients with incident diabetes [79].

Several potential mechanisms could explain the association between ACEi/ARB administration and decreased risk of mortality. ACEi/ARB treatment decreases the severity of left ventricular hypertrophy, dilation, remodelling, and HF commonly seen in CKD, and their treatment could contribute to lower cardiovascular risk [80]. In addition, ACEi/ARBs are renoprotective in patients with CKD, which could indirectly provide survival benefits [8, 10, 25]. ACEi/ARB administration is associated with a substantially larger survival benefit in diabetic patients compared with nondiabetic patients. Patients with CVD, HF, and hypertension may overpopulate the diabetic cohort resulting in the larger apparent benefit from ACEi/ARB treatment in this subgroup. Another potential mechanism is the anti-inflammatory effect of RAAS modulation, which could be especially important in this group of patients in whom inflammation is likely more prevalent than in non-CKD populations [81].
A recent retrospective cohort study of 55,266 CKD patients from a US group found that a serum potassium >6 mmol/l was prevalent in 1.8% of patients with an eGFR of <30 ml/min and both hyperkalaemia and hypokalaemia were associated with increased rates of death/MACE/hospitalisations and discontinuation of RAAS blockade. The adjusted mortality for patients with a serum potassium >6 mmol/l was 3.08 (2.17–4.37), MACE 2.11 (1.68–2.65) and discontinuation of RAS blockade 1.81 (1.45–2.26) in comparison to patients with potassium <6 mmol/l [82].

**Questions That STOP ACEi/ARBs May Answer**

Studies suggesting that ACEi/ARBs are renoprotective in patients with CKD have formed the basis of guidelines which recommend the use of ACEi/ARBs in patients with proteinuria with or without diabetes, even with albuminuria as low as 30 mg/mmol/day. This recommendation has been transposed to apply to advanced CKD. Trial evidence on the effectiveness and safety of ACEi/ARB discontinuation in advanced CKD is lacking. This is reflected in current guidelines, which provide no specific instructions regarding ACEi/ARBs in relationship to the severity of CKD [83].

Patients with high activation of RAAS theoretically stand to benefit more from the cardio-protective and antiproteinuric effect of ACEi/ARB but are also likely to experience the greatest increase in glomerular filtration rate with RAAS blockade cessation. Renoprotection from ACEi/ARBs may in fact be lost in advanced CKD when significant ischaemic nephropathy is present. This hypothesis is supported by reports in both diabetic and non-diabetic patients with CKD that ACEi/ARBs may accelerate the progression of CKD into ESRD and RRT through intrarenal haemodynamic effects [13, 84]. In addition, cardiovascular events are more common in dialysis than pre-dialysis patients suggesting the increased importance of avoiding dialysis therapy, which accelerates cardiovascular risk.

A recent observational study from Ahmed et al. has demonstrated that ACEi/ARB withdrawal in 52 patients (21 female, 31 male) with advanced CKD led to an overall mean increase in eGFR of 10 ml/min/1.73 m² over 12 months (eGFR 16.38 vs. 26.6 ml/min/1.73 m², p < 0.01), and an increase or stabilisation in eGFR in all but 4 patients. A modest change in BP was also observed (mean arterial pressure 90 vs. 94 mm Hg, p = 0.02) with no increase in cardiovascular events and no change in proteinuria (77 vs. 121.6 mg/mmol; p = NS) [85].

There is further evidence of the problems associated with ACEi/ARB in advanced CKD and predialysis patients from a retrospective cohort study, which evaluated risk factors for adverse drug events and found factors such as hyperkalaemia and renal impairment as indications for discontinuation of medication [86]. In this study of 2,225 out-patients administered ACEi, 19% of the initial group discontinued ACEi therapy due to adverse events.

There remains a double-edged sword of ACEi/ARB discontinuation to maintain eGFR but worsen cardiovascular morbidity. The challenge of separating cause and effect and selection bias for those patients who might not have underlying CVD remains [14]. However, the majority of these patients die before needing RRT from other causes including CVD. Whether treatment with ACEi/ARB could change this outcome is unknown.

Neovius et al. [31] have shown that there is an increase in mortality for patients undergoing dialysis in comparison to those with non-dialysis dependent CKD. This has been observed in other registry data [27]. This supports the hypothesis of benefit to delaying the start of RRT. This Swedish national healthcare system population-based cohort study compared patient mortality between CKD stages 4 and 5 (n = 3,040; mean age 66 years), peritoneal dialysis (n = 725; 60 years), haemodialysis (n = 1,791; 62 years) and renal transplantation (n = 606; 48 years). After 6,553 person-years, those with CKD stages 4 and 5 had a considerably lower mortality risk (12 deaths/100 person-years, 95% CI 11–13) than dialysis patients (peritoneal dialysis (17 deaths/100 person-years, 95% CI 15–19), haemodialysis (25 deaths/100 person-years, 95% CI 23–27)). In direct comparison vs. CKD, the mortality HR was 1.7 (95% CI 1.4–2.1) for peritoneal dialysis, and 2.6 (95% CI 2.3–2.9) for haemodialysis [31].

A number of studies that have shown that rate of decline of kidney function as measured by eGFR is associated with worse clinical outcomes, including all-cause mortality [18, 68, 87]. We have also demonstrated in a retrospective study of 273 patients with a mean eGFR of 20.8 ml/min/1.73 m², that a rapid decrease in eGFR of >4 ml/min/1.73 m² is predictive of the need for RRT (p < 0.001) and increased mortality (p = 0.07) [88].

As GFR falls <30 ml/min (stages 4–5) vascular architecture changes, vessels stiffen and calcify, statins lose their effectiveness, the heart often fails and evidence for clinical decision making becomes scanty. Currently, there is no clear evidence of reduced or increased cardio-protective effect of ACEi/ARB use in patients with advanced
CKD although there is some post hoc evidence for those with HF.

One size does not fit all in relation to real-life optimal clinical management, and recent guidelines from KDIGO in other areas recommend individualised care [89]. The STOP ACEi trial will increase the evidence based to future clinical practice as this trial is stratified for age, diabetes and proteinuria. STOP ACEi will also provide further evidence in the management of those patients with heavy proteinuria, salt and water overload and congestive HF.

The STOP ACEi trial is a multicentre, open-label, randomised, controlled clinical trial, which aims to answer the question of whether stopping ACEi/ARB results in a stabilisation or improvement in renal function in patients with advanced progressive CKD [24]. Secondary outcomes will exam cardiovascular events.

Conclusions

Currently, there is a state of equipoise about the use of ACEi/ARBs in patients with advanced CKD. There is uncertainty as to whether the potential improvements in mortality and morbidity brought about by delaying ESRD and RRT conferred by cessation of ACEi/ARB offset any increase in CVD by their omission. The aim of STOP ACEi is to answer this question and will be of huge clinical importance to both patients and clinicians and could also have significant implications for healthcare budgets.

Disclosure Statement

The authors have no conflicts of interest to declare.

References


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