Progress in retarding the progression of advanced chronic kidney disease: Grounds for optimism

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It has been generally held that once glomerular filtration rate (GFR) falls below approximately 25 ml/min, a relentless progression to end-stage renal disease (ESRD) inevitably ensues, regardless of the original cause of reduced function. There is a paucity of contemporary studies, however, addressing whether the rate of progression can be slowed down with contemporary and comprehensive renal care when chronic kidney disease (CKD) has progressed to stages 4 and 5 (GFR $<$ 30 ml/min/1.73 m^2). In this review we argue that significant progress is being made already in retarding the progression of advanced CKD thereby delaying the initiation of renal replacement therapy. We propose that CKD clinics, by providing comprehensive management of CKD, will have a decisive role in preventing and delaying the progression to advanced CKD.

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Chronic kidney disease (CKD) is associated with increased morbidity and mortality. An estimated 7.6 million adults in the United States have stage 3 CKD glomerular filtration rate (GFR 30–59 ml/min/1.73 m^2) and about 700 000 have stages 4 and 5 combined (GFR $<$ 30 ml/min/1.73 m^2).[1] Around 250 000 are on dialysis, whereas the remaining 450 000 patients with stages 4 and 5 are close to initiation of renal replacement therapy including kidney transplantation.[2]

It has been generally held that once GFR falls below approximately 25 ml/min, a relentless progression to end-stage renal disease (ESRD) inevitably ensues, regardless of the original cause of reduced function.[3–6] Recent clinical trials and observational studies on the progression of CKD have usually not focused on patients with advanced stages of CKD.[7,8] In fact patients with advanced renal insufficiency were excluded from large-scale, prospective, randomized clinical trials that have shown renin–angiotensin system inhibitors to be more renoprotective than other antihypertensive classes. This exclusion was largely owing to the concerns with the risk of acute renal failure and hyperkalemia. However, in animal models of chronic nephropathy, renin–angiotensin system inhibitors are renoprotective even when the disease is advanced.[9] There is a paucity of studies addressing whether the rate of progression can be slowed down with contemporary renal care when CKD has progressed to stages 4 and 5 (GFR $<$ 30 ml/min/1.73 m^2).

In this article, we review data from selected clinical studies which included patients with advanced CKD. Although the study design the objectives, and the interventions were different, the analyses of those studies give us an idea of the rate of GFR loss over a follow-up of about 3 years.[10–12] An important concept that emerges from two of these studies is that patients do benefit from interventions such us the use of angiotensin-converting enzyme (ACE) inhibitors even in advanced stages of CKD.[11,12] Moreover, we argue that stabilization of GFR is possible in many patients with advanced CKD, an outcome which would appear elusive until recently. A study from a CKD clinic, of a cohort of 82 patients with advanced CKD, stages 4 and 5 followed for 2 years since initiation of erythropoietin therapy showed stabilization of GFR in more than 50% of patients.[13] We therefore propose that CKD clinics will have a decisive role in preventing and delaying the progression to advanced CKD.

Table 1 | Summary of selected key studies on advanced CKD

Trial	Type	Duration (years)	Sample size	Baseline GFR level (ml/min per 1.73 m^2)	Strategy	Outcome
MDRD Hunsicker *et al.*[11]	*Post hoc* analysis	3.5	255	13–24 ml/min (Group B only)	Tight BP control, dietary protein restriction.	Rate of loss of GFR of 4 ml/min/year.
REIN Ruggenenti *et al.*[12]	*Post hoc* analysis	2.7	107	10.5–32.7 ml/min (Lowest tertile)	BP control using ACE inhibitor (Ramipril) vs conventional therapy.	ACE (Ramipril) decreased rate of GFR decline (Delta GFR) by 22% in the lowest tertile GFR(10.5–32.7 ml/min).
Hou *et al.*[10]	Randomized double-blind study	3.4	224	25.8 $\pm$ 5.3 ml/min (Group 2 only)	Benezapril or placebo along with conventional anti-hypertensive therapy.	Median rate of GFR decline: 6.8 ml/min/1.73 m^2/year with benazepril, as compared with 8.8 ml/min/1.73 m^2/year among the patients assigned to placebo.
Serrano *et al.*[13]	Longitudinal follow-up in a CKD clinic	2.0	82	10–29 ml/min (Av 18.8 $\pm$ 5.5)	Initiation of anemia management in a CKD clinic using EPO.	Mean GFR decreased at a significantly lower rate in the group without primary outcomes compared to the group that developed outcomes (0.08 ml/min/1.73 m^2 vs 0.43 ml/min/1.73 m^2, P=0.007).

ACE, angiotensin-converting enzyme; BP, blood pressure; CKD, chronic kidney disease; EPO, erythropoietin; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; REIN, Ramipril Efficacy In Nephropathy.

In this context, we summarize and contrast our outcomes in our CKD clinic, with the results of controlled studies involving subjects with advanced CKD (Table 1).

REVIEW OF SELECTED CLINICAL STUDIES INVOLVING SUBJECTS WITH ADVANCED CKD

A subsequent analysis of data from the Modification of Diet in Renal Disease by Hunsicker *et al.*[11] involved a subgroup of patients with low GFR (13–25 ml/min/1.73 m^2). In this subgroup the rate of progression (GFR loss) was 4 ml/min/year in the face of dietary protein restriction and 'strict blood pressure' control. It should be noted that participants in the Modification of Diet in Renal Disease study were not receiving ACE inhibitors or erythropoietin.[11] Thus, the overall care for CKD has evolved markedly since the Modification of Diet in Renal Disease study was completed more than 12 years ago. Accordingly, one would expect a better outcome in more recent studies.

In the Modification of Diet in Renal Disease study there was a large variability in the rates of progression between different individuals at all levels of initial GFR, with slopes ranging from positive (increases in GFR over time) to negative values (indicating GFR decline) as great as 10 ml/min/year in the patients with most rapid progression.[11] Interestingly, in about 11% of patients in study B with at least 1-year follow-up, the GFR levels were stable or improving, suggesting stabilization of renal function and arguing against the inevitability of progression to advanced CKD once renal insufficiency begins.

The Ramipril Efficacy In Nephropathy, was a large-scale study, that included patients with advanced renal insufficiency.[14] It was designed to evaluate the renal effects of the ACE inhibitor ramipril in proteinuric non-diabetic chronic nephropathies and to prospectively investigate the main clinical determinants of progression and response to treatment.[14] It attempted to address the relationship between protein excretion and renal-disease progression and also to find out, whether an ACE inhibitor was superior to conventional treatment, with the same blood-pressure control, in reducing proteinuria, limiting GFR decline, and preventing ESRD. The Ramipril Efficacy In Nephropathy study showed that renin–angiotensin system inhibition slows GFR decline over time and progression to ESRD. Ramipril significantly lowered the rate of reaching the combined end point of doubling of baseline serum creatinine levels or end-stage renal failure (ESRD). In a subsequent *post hoc* secondary analysis of Ramipril Efficacy In Nephropathy,[12] the impact of baseline renal function (GFR 10–100 ml/min/1,73 m^2) on disease progression and response to treatment was evaluated. ACE inhibition risk/benefit profile was assessed in 322 patients (mean follow-up of 31 months) with non-diabetic, proteinuric chronic nephropathies and different degrees of renal insufficiency. The patients were divided into three tertiles according to baseline GFR. Within each tertile, ramipril slowed the rate of loss of GFR (by 22, 22, and 35% in the lowest (10.5–32.7 ml/min), middle, and highest tertiles, respectively). The incidence of ESRD was also reduced by 33% ($P<0.05$), 37, and 100% ($P<0.01$) in the lowest, middle, and highest tertiles, respectively, as compared to conventional anti-hypertensive treatment (non-ACE inhibitors and angiotensin II receptor blockers).[12] The risk of ESRD and the absolute number of events saved by ACE inhibition was highest in patients with the lowest GFR.[12] Disease progression and response to ACE inhibition did not depend on severity of renal insufficiency, with ACE inhibition uniformly slowing GFR decline and progression to ESRD