The rationale for early management of chronic renal insufficiency

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Abstract
Several strategies are available to delay progression of renal disease and the development of associated co-morbidities. Hypertension is a strong independent risk factor for end-stage renal disease (ESRD) and there is consensus that blood pressure (BP) management is an important aspect of care in patients with chronic renal insufficiency (CRI). Clinical studies have shown that angiotensin-converting enzyme (ACE) inhibitors have renoprotective properties, independent of their antihypertensive effects, which can delay the onset of ESRD. Studies have also shown that intensive therapy of both type 1 and type 2 diabetes patients, to give near normal blood glucose concentrations, can reduce the incidence of progressive clinical proteinuria and may, therefore, protect against ESRD. Additionally, data are emerging that treatment of renal anaemia with epoetin can reduce mortality and delay the onset of dialysis in CRI patients, but these encouraging results need to be confirmed in large prospective studies. In conclusion, control of BP and hyperglycaemia, as well as use of ACE inhibitors and anaemia treatment, all have potential in delaying the progression of CRI or improving patient outcomes. If benefit is proven in future studies, these strategies will be most effective if implemented early in the course of CRI.

Keywords: ACE inhibitors; anaemia; chronic renal insufficiency; diabetes; hyperlipidaemia; hypertension

Introduction
There is a high rate of late referral among patients with progressive renal failure, which reduces the chance of detecting correctable disorders [1,2]. In addition, in patients with chronic renal insufficiency (CRI), delayed referral reduces the opportunity for preparing the patient for dialysis or transplantation [1–3], and has a negative impact on patient survival and other clinical outcomes [4,5]. Late referral also contributes to the considerable, escalating costs of end-stage renal disease (ESRD) management. There is a need, therefore, to identify and effectively manage patients early in the course of CRI.

There are many reasons why patients are being referred late, including possible referral bias, lack of availability of specialist care in certain areas and, most importantly, physician ignorance and apathy [1,2]. Many physicians are unaware of the potential benefits of early management of CRI and there is a need for improved education in this area.

Not all patients with CRI will progress to ESRD and it is important that those patients with progressive illness be identified. The presence of diabetes mellitus, microalbuminuria and essential hypertension are all adverse risk factors for the progression of renal disease [2]. Currently, it is unclear whether the presence of overt proteinuria is an adverse risk factor that can be modified to improve treatment outcome; it may already be too late to intervene to halt the progression of CRI in patients presenting with this condition.

Therefore, the objectives of treatment strategies for patients with CRI are to halt or delay progression of renal disease and its associated co-morbidities. Several such strategies are available, including control of hypertension, use of angiotensin-converting enzyme (ACE) inhibitors, treatment of proteinuria, control of diabetes, dietary protein restriction, control of hyperlipidaemia, and management of renal anaemia. These strategies are discussed in the following sections.

Control of hypertension
It is becoming increasingly clear that control of hypertension is of major importance in patients with CRI to minimize the progression of renal failure and to decrease the risk of cardiovascular complications associated with renal failure [3]. For example, Klag et al. [6] assessed the development of ESRD over a 16-year period in over 330,000 men screened for the Multiple Risk Factor Intervention Trial (MRFIT).
Higher blood pressure (BP) was a strong independent risk factor for ESRD; even patients with BP considered to be at the higher end of the normal range had a significantly increased risk of ESRD (Table 1).

Various classes of pharmacological agents are available to treat hypertension but the optimal degree of BP lowering necessary to prevent complications of hypertension is still unclear [7]. The Hypertension Optimal Treatment (HOT) study assessed the association between three target diastolic BP (90, 85 and 80 mmHg) during antihypertensive therapy and the incidence of major cardiovascular events [7]. All patients were treated with felodipine. Additional therapy (ACE inhibitors and beta-blockers) and dose increments were prescribed to reach target BP. The study clearly showed that it is possible to achieve respectable systolic and diastolic BPs in patients with essential hypertension using the currently available pharmacological agents. The majority of patients, however, required multiple drug regimens, as demonstrated in patients with CRI [8].

The HOT study found that lowering BP to 85 mmHg or lower was associated with a reduction in the incidence of major cardiovascular events [7]. Further BP lowering gave little additional benefit but did not cause any significant increased risk. Active lowering of BP was of particular benefit in the subgroup of patients with diabetes. There was a significant reduction (51%) in the incidence of major cardiovascular events in the lowest BP target group compared with the highest BP target group among patients with diabetes (P<0.005). A more recent analysis of data from the HOT study examined the relationship between cardiovascular events and baseline renal function, and concluded that cardiovascular events were more frequent among patients with mild renal insufficiency (baseline creatinine clearance <60 ml/min) in all BP target groups, irrespective of the treatment offered [9].

Dasgupta et al. [3] examined the quality of BP control in 145 patients admitted to a dialysis programme over a 3-year period. Hypertension was present in 76% of patients before they developed ESRD but deviations in standards of care were common. The British Hypertension Society diastolic BP target (90 mmHg at the time the study was conducted) was achieved in only 45% of patients. Independent assessment of the data suggested that poor BP control had probably contributed to the progression of renal failure in 32% of patients. Recommended standards for detection, investigation, control, follow-up and referral were often not achieved. Thus, despite the consensus that management of BP is an important aspect of care in CRI patients, there is evidence of poor BP control in many patients with CRI.

Use of ACE inhibitors and control of proteinuria

ACE inhibitors may have kidney-protecting properties independent of their antihypertensive effect. In addition, ACE inhibitors can reduce urinary protein excretion in patients with diabetic and other nephropathies [10].

A US randomized, placebo-controlled collaborative study of type 1 diabetes patients with nephropathy was designed to evaluate the effects of the ACE inhibitor, captopril (25 mg three times daily), on renal function [10]. Median follow-up was 3 years. All patients had a serum creatinine concentration of <2.5 mg/dl and urinary protein excretion of ≥500 mg. Target BP was <90 (diastolic) and <140 mmHg (systolic).

The percentage of patients with a doubling of baseline creatinine to at least 2 mg/dl was significantly lower in the captopril group than the control group (Figure 1). This benefit was evident within the first year of administration of captopril. Similarly, the percentage of patients requiring dialysis, transplantation or who died during the study was significantly lower in the captopril group (11%) than the placebo group (21%). A significant reduction in the rate of deterioration of renal function was also observed in the captopril group. These beneficial results for captopril were observed despite comparable BP control in the two groups and suggest that, for diabetic nephropathy at least, ACE inhibitors can slow disease progression by a mechanism independent of their antihypertensive properties.

The Ramipril Efficacy in Nephropathy (REIN) study evaluated the benefits of an ACE inhibitor in non-diabetic patients with renal disease [11]. Patients (n = 352) were stratified at baseline into a low urinary

<table>
<thead>
<tr>
<th>BP category (systolic/diastolic mmHg)</th>
<th>Patients (n)</th>
<th>Adjusted relative risk (95% CI)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Optimal (&lt;120/&lt;80)</td>
<td>61089</td>
<td>1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Normal (120–129/80–84)</td>
<td>81621</td>
<td>1.2 (0.8–1.7)</td>
<td>NS</td>
</tr>
<tr>
<td>High normal (130–139/85–89)</td>
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<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1 (140–159/90–99)</td>
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</tr>
<tr>
<td>Stage 2 (160–179/100–109)</td>
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<td>Stage 3 (180–209/110–119)</td>
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<tr>
<td>Stage 4 (≥210/≥120)</td>
<td>1429</td>
<td>22.1 (14.2–34.3)</td>
<td>&lt;0.001</td>
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protein excretion group (1–3 g/24 h) and a high urinary protein excretion group (≥3 g/24 h) and then randomly assigned to ramipril or placebo plus conventional antihypertensives to achieve a target diastolic BP of <90 mmHg. In the high urinary protein excretion group, there was a significant improvement in the rate of decline of glomerular filtration rate (GFR) in patients treated with ramipril compared with patients treated with placebo. Urinary protein excretion significantly decreased from baseline in the ramipril group over the first month of treatment and remained below baseline throughout the study. In contrast, urinary protein excretion did not change significantly during the study in the placebo group.

Only 23% of patients in the ramipril group compared with 45% of patients in the control group reached the combined endpoint of a doubling of baseline serum creatinine concentration or development of ESRD (P = 0.02). The renoprotective effect of ramipril was independent of baseline or follow-up BP and the authors suggested that this effect could result from a partial limitation of protein traffic and consequent reduced toxicity to the kidney [11].

A subsequent 4–5-year follow-up study of patients from the high urinary protein excretion group of the REIN study has been reported by Ruggenenti et al. [12]. Patients in the control group were switched to ramipril plus conventional antihypertensive therapy to maintain diastolic BP <90 mmHg. Patients randomized to the original ramipril group showed an initial progressive decrease in GFR but after 3 years of continued treatment, GFR began to improve progressively up to the last follow-up point. Patients in the original placebo group showed a steady decline in GFR. After switching to ramipril, the decline in renal function tended to slow down and seemed to stabilise during the last year of follow-up. This suggests that ACE inhibitors are able to partially reverse renal damage even in patients with moderately advanced renal failure. However, starting treatment early in the course of CRI is likely to result in greater improvements in renal function than delaying treatment.

Additionally, a meta-analysis has been performed on data from 10 trials evaluating the effects of various ACE inhibitors compared with other antihypertensives on the progression of non-diabetic renal disease. The results of the meta-analysis support the positive benefits of ACE inhibitors in delaying the onset of ESRD. There was a 30% reduction in the relative risk of developing ESRD in patients treated with ACE inhibitors compared with conventional antihypertensives [13].

Despite the well-documented benefits of ACE inhibitors in patients with CRI, many are still not prescribed these agents. A recent report of 201 patients attending an outpatient clinic showed that only about 60% of CRI patients were actually prescribed ACE inhibitors [8]. Surveys of other renal populations have also shown a low prescription rate of ACE inhibitors [14].

Control of diabetes

The Diabetes Control and Complications Trial (DCCT) found that intensive treatment of type 1 diabetes patients to achieve near normal blood glucose and glycosylated haemoglobin concentrations resulted in a significant reduction in the incidence of microvascular complications when compared with conventional therapy [15]. The Epidemiology of Diabetic Interventions and Complications (EDIC) study followed up the 1441 patients originally enrolled in the DCCT to assess whether these benefits were sustained [16].

Patients originally treated with conventional therapy were offered treatment with the intensive regimen.
During the 4-year follow-up, the frequency of progressive microalbuminuria and clinical proteinuria remained substantially lower in the former intensive therapy group than the conventional therapy group. There was a 53% reduction in new-onset microalbuminuria and an 86% reduction in the rate of clinical proteinuria among patients in the intensive therapy group. The beneficial effects of intensive therapy were evident despite worsening hyperglycaemia during the follow-up period.

The Steno Trial also evaluated intensive vs standard treatment but in 160 patients with type 2 diabetes and microalbuminuria [17]. Intensive treatment involved behaviour modification and pharmacological therapy for hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria. Patients in the standard treatment group were managed by their general practitioner according to recommendations of the Danish Medical Association. Targets for BP and glycosylated haemoglobin, cholesterol and triglyceride concentrations were all substantially lower in the intensive therapy group than in the conventional group. In addition, ACE inhibitors were prescribed irrespective of BP and aspirin was prescribed for peripheral vascular disease in patients in the intensive therapy group but not the conventional group.

Over the course of the 4-year study, the likelihood of progression to nephropathy, retinopathy and autonomic neuropathy were all significantly lower with intensive therapy compared with conventional therapy (Figure 2). Ten per cent of patients in the intensive therapy group and 24% of patients in the conventional group developed nephropathy during follow-up ($P = 0.01$).

These trials clearly show that a prolonged period of intensive therapy to produce nearly normal blood glucose concentration is able to delay or prevent the earliest manifestations of diabetic nephropathy, without inducing severe side effects [16,17]. In addition, intensive therapy is likely to be more effective when started within the first 5 years of diabetes onset rather than when started as a secondary intervention after complications have already developed [15,16]. In practice, however, this level of control of hyperglycaemia is likely to be difficult to achieve and maintain. Further research is required in this area to determine how this strategy can be best implemented on a wider scale.

**Dietary protein restriction**

Dietary protein restriction in CRI patients has been the subject of clinical trials in a number of countries, with restriction to 0.4–0.6 g/kg body weight being associated with a modest reduction in the rate of CRI progression [18]. The magnitude of this benefit is relatively small when compared with that of ACE inhibitors and appears to be largely confined to patients with chronic glomerular diseases, such as diabetes and hypertension.

Restriction of protein to low levels is likely to be difficult to achieve and maintain in most patients, and is also likely to compromise nutrition. Patients may even require ketoacid supplementation, but, in some countries, the lack of availability and the expense of ketoacid supplements mean this is not always a viable option. Most nephrologists, therefore, advise a more modest degree of protein restriction (0.8–1.0 g/kg body weight), despite the knowledge that this level will not achieve the maximal benefit.

**Control of hyperlipidaemia**

Few studies have been performed to investigate the impact of hyperlipidaemia management on delaying the progression of CRI. However, animal studies...
suggest that control of hyperlipidaemia can influence the progression of renal disease [19] and the few human studies that have been carried out have suggested that lipid-lowering therapy may slow deterioration in GFR [20], although these results need to be confirmed in large, randomized trials.

It has been suggested that elevations in apoprotein B concentration may be associated with rapid progression of CRI [21]. In addition, lipid abnormalities in renal allograft recipients have been associated with poorer renal function and a more rapid rate of disease progression [22]. However, no studies of reasonable size have addressed specifically whether reversal of lipid abnormalities is of benefit in patients with renal disease. Nevertheless, hyperlipidaemia should be managed in patients with CRI with the primary aim of improving cardiovascular outcomes.

Anaemia management

Anaemia is common in patients with CRI and it is well established that its treatment with recombinant erythropoietin (epoetin) offers substantial clinical benefits in terms of improvements in quality of life and reductions in morbidity and mortality [23].

Two recent studies have assessed whether early treatment of anaemia in patients with CRI can influence positively the rate of disease progression. Jungers et al [24] performed a retrospective study of the rate of decline of creatinine clearance and the duration of the pre-dialysis period in 63 patients with CRI, 20 of whom had renal anaemia (mean haemoglobin concentration, 8.8 g/dl) and received epoetin treatment. The remaining 43 had a similar degree of chronic renal failure but had asymptomatic anaemia (mean haemoglobin concentration, 10.9 g/dl) and did not receive epoetin.

At baseline, the mean rate of decline of creatinine clearance was 0.36 ml/min/1.73 m²/month in the epoetin group, and at the end of the 2-year follow-up, the mean rate of decline was significantly lower (0.26 ml/min/1.73 m²/month), suggesting that epoetin treatment had a renoprotective effect. No significant variation was observed between baseline and at 2-year follow-up in the control group. In addition, epoetin treatment significantly delayed the start of dialysis. The mean time to start of dialysis was 16.2 months in the epoetin group compared with 10.6 months in the control group (P < 0.01). These results are contrary to those of animal studies that have suggested epoetin use may accelerate the deterioration to ESRD [25]; epoetin did not cause progression of CRI in any of the pre-dialysis patients treated.

A second study of epoetin was a retrospective cohort study, evaluating the impact of epoetin treatment initiated during the pre-dialysis period on the subsequent incidence of mortality in patients who had progressed to ESRD [26]. Of the 4866 patients evaluated, 22.7% had received epoetin during the pre-dialysis period. The risk of death was significantly lower for patients who received pre-dialysis epoetin than for patients who were not treated (relative risk 0.8). The survival benefit was most significant in patients with the highest haematocrit at the start of dialysis (Table 2). This study suggests that pre-dialysis use of epoetin can reduce the mortality rate in patients with progressive renal disease, especially in those with an adequate haematocrit response.

Conclusions

There are several strategies that can be implemented to influence the progression of CRI and associated co-morbidities. Clinical studies support the benefit of controlling hyperglycaemia in patients with diabetic nephropathy. There are also excellent epidemiological data supporting the role of antihypertensive agents in CRI, although these encouraging results need to be confirmed in randomized, controlled trials. It is increasingly evident that ACE inhibitors can slow progression of renal disease by a mechanism that is independent of their antihypertensive properties. Several trials are currently investigating the role of ACE inhibitors and angiotensin receptor antagonists in CRI and the results of these are eagerly anticipated. Randomized, controlled trials also support dietary protein restriction in CRI but the benefit is small and possibly diminished by the compromised nutrition that may result. Finally, preliminary evidence suggests that anaemia management plays an important role in delaying or halting progression of CRI and its associated co-morbidities. At present, however, anaemia management strategies remain suboptimal. There is still debate over the target haematocrit that should be achieved in patients with CRI and there is a need for prospective randomized trials to confirm the encouraging results suggesting that epoetin treatment can delay progression of CRI.

Thus, control of hypertension and hyperglycaemia, use of ACE inhibitors and anaemia treatment all have potential for improving patient outcomes if implemented early in the course of CRI, by delaying the progression of the disease and associated

<table>
<thead>
<tr>
<th>Haematocrit (%)</th>
<th>Relative risk of death (95% CI)</th>
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<tr>
<td>&lt;23.1</td>
<td>0.76 (0.53–1.07)</td>
</tr>
<tr>
<td>23.1–26.2</td>
<td>0.79 (0.60–1.07)</td>
</tr>
<tr>
<td>26.3–28.7</td>
<td>1.02 (0.78–1.04)</td>
</tr>
<tr>
<td>28.8–31.8</td>
<td>0.81 (0.64–1.09)</td>
</tr>
<tr>
<td>&gt;31.8</td>
<td>0.67 (0.51–0.89)*</td>
</tr>
<tr>
<td>Overall (n = 1107)</td>
<td>0.80 (0.70–0.91)</td>
</tr>
</tbody>
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*P < 0.01.
co-morbidities. Future research will determine the best intervention strategies to achieve optimal benefit in the maximum number of patients.

References