Risk Factors for the Development and Progression of Renal Diseases in Disadvantaged Populations: Role of the Renin-Angiotensin System Blockade

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Chronic kidney disease is becoming a public health challenge due to the high risk of progression to end-stage kidney disease, the increased cardiovascular burden and management costs, especially among disadvantaged communities. Although the high prevalence of hypertension and diabetes in these populations are recognized risk factors and a leading cause of chronic kidney disease, ethnic populations show a greater likelihood of developing end-stage kidney disease regardless of these cardiovascular risk factors. The association between low socioeconomic status and the prevalence/progression of chronic kidney disease observed in population-based studies suggests that socioeconomic disadvantage could be a plausible reason for the increased burden of renal disease among minorities. Interventions for management and prevention of chronic kidney disease include angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Few studies of these agents have been conducted in indigenous populations, but there is evidence that angiotensin converting enzyme inhibitors are effective in reducing premature deaths and progression of chronic kidney disease, as well as being highly cost-effective, especially in terms of renal replacement therapies avoided. It is plausible that these disadvantaged groups may benefit more than others from a renal and cardiovascular prevention program, but considerable under-recognition and under-treatment of these conditions still exist. (*Ethn Dis*. 2009 [Suppl 1];19: S1-86–S1-89)

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Background

Chronic kidney disease (CKD) is a medical and public health challenge. There have been variable definitions of CKD, and a review of population-based data, which defined CKD as glomerular filtration rate <60 mL/min/1.73 m^2, found that 7.2% of people aged ≥ 30 years and 23.4%–35.8% of people aged ≥ 64 years were affected by CKD.[1]

Studies have found that patients with CKD may have a high risk of progression to end-stage renal disease (ESRD), requiring dialysis or renal transplantation for renal replacement therapy. CKD and ESRD are associated with excess cardiovascular mortality and morbidity.[2]

Hypertension and diabetes are well-established causes of kidney disease. Data from a community-based ($N = 23{,}534$) prospective observational study[3] of 20 years' duration show that the incidence of CKD increases 3- to 9-fold per category increase in blood pressure, according to the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure blood pressure categories.[4] CKD associated with diabetes, also called diabetic nephropathy or diabetic kidney disease, involves the presence of microalbuminuria or macroalbuminuria and occurs in a large proportion of diabetic patients (25%–40%). In addition, having diabetes is associated with an odds ratio for end-stage renal disease of 11.1 (95% confidence interval [CI] 7.2–16.9).[5] Hypertension and diabetes are also associated with excess cardiovascular morbidity and mortality independently and in the presence of renal disease.

Ethnicity and Chronic Kidney Disease

Sociodemographic status and ethnicity have received attention for being associated with an increased risk of adverse vascular outcomes, including cardiovascular events and mortality. Data from the United States Renal Data System show that the risk of progression from CKD to ESRD is significantly higher among ethnic minorities compared with the general population, and incidence rates in some groups are up to 4 times higher than in Whites.[6] Although diabetes and hypertension are the leading causes of CKD, and Blacks and other minorities are more likely to have diabetes and hypertension, these ethnicities have a greater probability of developing ESRD regardless of the presence of these 2 risk factors[7] (Table 1).

The association between low socioeconomic status and the prevalence and progression of CKD has been widely observed in population-based studies,[8–11] which suggests that socioeconomic disadvantage could be a reason for the increased prevalence of renal disease among minorities. Results of an ecological study performed in the 36 Aboriginal and Torres Strait Islander Commission regions of Australia showed a strong association between area-based measures of disadvantage and the regional incidence of ESRD in indigenous Australians (Table 2).[12]

Recent data indicate that compared with a population of age- and sex-matched nonindigenous children, Aboriginal children in Australia had no increase in albuminuria, proteinuria, or persistent hematuria, the most important markers for CKD; they suggested that ESRD in aboriginal people may therefore be preventable during early life.[13] We should aim to broadly

Table 1. Age-adjusted risk of end-stage renal disease by sex and ethnicity. (Table reprinted with permission from Xue et al., *J Am Soc Nelphrol*. 18 (4): 1299–306, 2007)

Characteristic	Hazard Ratio (95% Confidence Interval)				
	Whites	Blacks		Other Ethnicities	
		Men	Women	Men	Women
Diabetes at baseline	1.0	2.12 (1.90–2.36)	2.50 (2.31–2.71)	1.41 (1.20–1.66)	1.90 (1.68–2.16)
Diabetes at followup	1.0	1.93 (1.61–2.33)	3.41 (2.94–3.95)	1.27 (.98–1.66)	2.01 (1.58–2.57)
No diabetes	1.0	2.27 (2.01–2.55)	3.53 (3.15–3.94)	1.55 (1.29–1.86)	1.95 (1.58–2.40)
Hypertension at baseline	1.0	2.05 (1.87–2.25)	2.82 (2.63–3.02)	1.37 (1.18–1.59)	1.93 (1.70–2.18)
Hypertension at followup	1.0	2.22 (1.90–2.60)	3.62 (3.17–4.13)	1.50 (1.21–1.86)	2.04 (1.68–2.49)
No hypertension	1.0	3.07 (2.51–3.76)	2.94 (2.28–3.80)	1.74 (1.32–2.30)	2.16 (1.58–2.95)
No diabetes or hypertension	1.0	3.27 (2.55–4.19)	4.03 (2.91–5.57)	1.83 (1.29–2.59)	2.24 (1.43–3.50)

improve adoption of standard preventive interventions that are recommended in the general population.

THERAPEUTIC STRATEGIES FOR PREVENTING PROGRESSION OF CKD

Intervention for management and prevention of CKD includes antihypertensive agents as a first line strategy. Data obtained from many large-scale trials conducted in hypertensive patients (ALLHAT, CAPP, HOT, INSIGHT, NORDIL, SHEP, STOP-Hypertension2, Syst-Eur) postulated that these patients (including a proportion of diabetic patients) should be treated with any antihypertensive agent, provided the blood pressure was lowered to <130/80 mm Hg. However, on the basis of relevant trials conducted in a population affected by diabetic nephropathy (IDNT, REIN, RENAAL, AASK, CAPTOPRIL TRIAL) key guideline agencies began to recommend angiotensin converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) as the best antihypertensive agents to treat hypertensive patients with diabetes and renal disease to prevent the progression from microalbuminuria or macroalbumuria to ESRD. These renin-angiotensin system inhibitors have been also tested among ethnic minorities, a high-risk group of patients with an increased prevalence of cardiovascular risk factors, and data support improved outcomes and cost-effectiveness.[14]

EVIDENCE ON THE BENEFITS AND HARMS OF ACE INHIBITORS AND ARBs

General Population

The efficacy of ACE inhibitors in the primary prevention of nephropathy was evaluated by a recent metaanalysis of 16 randomized controlled studies (7603 patients) of ACE inhibitors versus placebo or other antihypertensive agents in patients with diabetes.[15] The objective of this systematic review was to compare the benefits and harms of any antihypertensive agent with placebo or another agent in patients with diabetes and normal albuminuria. Compared with other agents, ACE inhibitors were the best choice for reducing the onset of microalbuminuria but not for doubling of

Table 2. Correlation between indicators of socioeconomic disadvantage and age- and sex-standardized incidence of end-stage renal disease for indigenous Australians for the 36 Aboriginal and Torres Strait Islander Commission regions[a]. (Table reprinted with permission from Cass, A., et al. *Ethn Dis*, 12(3), 373–378, 2002)

Socioeconomic indicator	Range	Correlation Coefficient	P value
Early school leavers[b] (%)	12.5–52.4	.68	<.001
Unemployment rate[c] (%)	20.2–74.8	.72	<.001
Household income[d] ($AUS)	80–194	−.71	<.001
House crowding[e]	1.1–3.2	.84	<.001
Low birth weight[f] (%)	7.6–21.6	.49	.003
Summary rank of disadvantage[g]	1–36	.88	<.001

[a] Aboriginal and Torres Strait Islander Commission regions are legally prescribed administrative areas and are the smallest geographical areas for which accurate Indigenous Australian population estimates are available (Australian Bureau of Statistics, 1999).

[b] The proportion of adults who left school aged 15 or less, or who did not attend school (Australian Bureau of Statistics, 2002).

[c] People employed through the Community Development Employment Projects scheme, a 'work for the dole' scheme targeted at indigenous communities, were classified as unemployed (Australian Bureau of Statistics, 2002).

[d] Median household income divided by the average number of persons per household—units are $AUS per household member per week (Australian Bureau of Statistics, 1998).

[e] The average number of persons per bedroom (Australian Bureau of Statistics, 2002).

[f] The proportion of births less than 2500 g (Day, Sullivan, & Lancaster, 1999).

[g] We combined the regional rankings on each indicator, with each indicator given equal weight, to derive a summary rank of disadvantage.

Table 3. Summary estimates of the effect of antihypertensive agents on renal, cardiovascular, and safety outcomes in patients with diabetes and diabetic nephropathy. (Table reprinted with permission from Strippoli et al, *J Am Soc Nephrol* 17,4 Suppl 2, S153-5, 2006).

Intervention	Outcome	No. of Trials	No. of Patients	RR (95% CI)
Primary prevention of nephropathy in patients with diabetes				
ACE inhibitor vs placebo	Onset of microalbuminuria*	6	3840	.60 (.43 to .84)
	Doubling of creatinine	3	2558	.81 (.24 to 2.74)
	ESRD	1	2683	2.35 (.46 to 12.10)
	All-cause mortality	4	3284	.81 (.64 to 1.03)
	Cough	4	3725	1.79 (1.19 to 2.69)
	Headache	1	2438	1.25 (.44 to 3.61)
	Hyperkalemia	2	2594	2.95 (.31 to 28.18)
ACE inhibitors vs calcium antagonist	Onset of microalbuminuria	4	1210	.58 (.40 to .84)
	All-cause mortality	6	1286	.84 (.26 to 2.73)
ACE inhibitor vs β-blocker	Onset of microalbuminuria	1	299	1.01 (.74 to 1.37)
Prevention of progression of nephropathy and other outcomes in patients with diabetic nephropathy				
ACE inhibitor vs placebo	All-cause mortality	20	2838	.79 (.63 to .99)
	Doubling of creatinine	8	1868	.60 (.34 to 1.05)
	ESRD	9	1907	.64 (.40 to 1.03)
	Microalbuminuria to macroalbuminuria	16	2010	.45 (.28 to .71)
	Microalbuminuria to normoalbuminuria	15	1888	3.42 (1.95 to 5.99)
	Cough	10	2269	2.74 (1.74 to 4.30)
	Headache	3	1326	.97 (.17 to 5.71)
	Hyperkalemia	2	1271	.85 (.35 to 2.08)
ARB vs placebo	All-cause mortality	4	3329	.99 (.85 to 1.17)
	Doubling of creatinine	4	3329	.79 (.67 to .93)
	ESRD	3	3251	.78 (.67 to .91)
	Microalbuminuria to macroalbuminuria	3	761	.49 (.32 to .75)
	Microalbuminuria to normoalbuminuria	2	670	1.42 (1.05 to 1.93)
	Cough	1	91	1.87 (.22 to 16.01)
	Headache	1	91	.47 (.03 to 7.22)
	Hyperkalemia	1	1148	5.41 (1.20 to 24.28)

RR = relative risk, CI = confidence interval, ACE = angiotensin-converting enzyme, ESRD = end-stage renal disease, ARB = angiotensin-receptor blocker.
* No effect modification for hypertensive vs normotensive participants.

creatinine or all-cause mortality (Table 3). These data support that if a patient has diabetes, ACE inhibitors are the only agents for which evidence exists of both cardiac and renal protection.

Another metaanalysis of 43 trials (7739 patients) explored the role of ACE inhibitors and ARBs versus placebo in patients with diabetic nephropathy.[16] Results of this review (Table 3) showed that, although both ACE inhibitors and ARBs significantly reduced the progression of renal disease, only ACE inhibitors were associated with a reduction of all-cause mortality. These data support that if a patient has diabetes and kidney disease (diabetic nephropathy), ACE inhibitors could be the first choice to prevent the progression of nephropathy and the risk of death and poor vascular outcomes until better evidence becomes available because the findings of these ACE inhibitor trials are close to being nonsignificant.

Data regarding the cardiovascular and renal effect of combined therapy with ACE inhibitors and ARBs have also been difficult to evaluate, because of the lack of patient-level renal endpoints such as ESRD or doubling of serum creatinine[17] and to problems with the design and power of available studies, in particular the COOPERATE trial, which was the authoritative trial until 2007.[18,19] Recent data published in 2008 from the large Ongoing Telmisartan Alone and in combination with Ramipril, Global Endpoint Trial (ONTARGET) triallist group[20] also poses relevant questions. The study (N = 25,620) found that in high-risk patients with history of cardiovascular events or diabetes and end-organ damage, there is no additional cardiovascular advantage with combination therapy (telmisartan plus ramipril) compared to full-dose monotherapy with ramipril alone, for a primary composite endpoint of death from cardiovascular causes, myocardial infarction, stroke, and hospitalizion for heath failure (combination therapy vs ramipril, relative risk [RR] .99, 95% CI .92–1.07). Moreover, results of this study showed the noninferiority of telmisartan compared with ramipril with respect to cardiovascular morbidity and mortality (telmisartan vs ramipril, RR 1.01, 95% CI .94–1.09). Unfortunately these data are insufficient to assess the specific role in patients with diabetes and renal disease; the study does enroll a large proportion of patients with microalbuminuria, of which many would be

diabetic, but data relating to this specific subset of patients are still unpublished and not available on request.

Indigenous Population

Key studies of ACE inhibitors were also conducted in indigenous populations. In a remote northern Australian region, the Tiwi Islands, a community-based cardiovascular and renal protective program was shown to be effective in reducing (by 50%) premature deaths and progression to ESRD (by 57%) among Aborigines, thanks to the strict control of blood pressure with ACE inhibitors as first-line therapy and control of diabetes with oral hypoglycemics and insulin.[14] However, there are some doubts about the extent of the reduction in adverse events in this study due to methodologic limitations.

The program was found to be highly cost-effective, providing cost savings especially in terms of avoiding the need for renal replacement therapy (dialysis) for ESRD.[21] For this reason, programs like this should be introduced and implemented in high-risk communities as a matter of urgency. An improvement in management of economic resources used for prevention programs and therapeutic strategies in order to slow down the burden of chronic kidney disease could be more promptly addressed in minorities, notwithstanding the existing difficulties.

CONCLUSIONS

There exists strong evidence that CKD and its progression to ESRD are increasing, especially among disadvantaged communities (eg, Australian Aborigines, Blacks, Hispanics) because of the high prevalence of cardiovascular risk factors (diabetes and hypertension) and low socioeconomic status, among other causes. These disadvantaged groups may benefit more than others from a renal and cardiovascular disease prevention program, but these conditions are considerably underrecognized and undertreated.

Strategies for preventing the onset of nephropathy and its progression in high-risk populations, such as diabetic patients, exist. Adoption of these evidence-proven strategies has resulted in a substantial improvement in the prevalence of CKD. Funds should be made available and more studies and public health programs conducted in disadvantaged communities in order to improve use of existing interventions (such as the inhibitors of the renin-angiotensin system) that will likely result in a reduction in the burden of CKD.

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