Renal risk scores: Progress and prospects

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Worldwide adoption of the Kidney Disease Outcomes Quality Initiative classification for chronic kidney disease (CKD) and widespread use of the estimated glomerular filtration rate to assess renal function have identified large numbers of patients with previously undiagnosed CKD. It is clear, however, that this is a heterogeneous group and that only a small minority of such patients ever progress to end-stage renal disease. There is thus an urgent need for a simple method of risk assessment that can be applied to all patients with CKD to identify those few at greatest risk. The magnitude of baseline proteinuria has long been recognized as an important predictor of renal prognosis. Furthermore, several studies have found that change in proteinuria after initiation of antihypertensive treatment as well as achieved level of proteinuria correlate with prognosis. Thus, proteinuria has emerged as the single most important marker of renal risk. Many other factors have been identified as risk factors for CKD progression. Several attempts have been made to combine a relatively small number of risk factors into a risk score to predict renal outcomes in specific groups of patients. Validation of these risk scores as well as further studies are now required to develop a renal risk score applicable to a more general population of patients with CKD. Similar methodology could be applied to assess the important issue of the cardiovascular risk associated with CKD.

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Heterogeneity with respect to outcomes is an almost universal phenomenon across the broad spectrum of human pathology due to complex interactions between genetic, environmental, and pathogenic factors. This has important implications for disease management and clinical decision making, which often requires careful assessment of the risks versus benefits of treatments or interventions. In many fields of medicine, risk evaluation has been formalized through the use of staging systems (particularly in oncology) or scoring systems, for example, the Framingham risk score to evaluate cardiovascular risk or the APACHE II score to assess prognosis in critically ill patients.

In nephrology, tools for assessing risk are still in their infancy. The past 5 years have seen welcome advances in efforts to raise awareness of chronic kidney disease (CKD) and its consequences. A uniform classification system proposed by the Kidney Disease Outcomes Quality Initiative has been adopted worldwide[1] and many laboratories now report estimates of glomerular filtration rate (GFR) derived from the 4-variable MDRD formula with each measurement of serum creatinine. Epidemiological studies have found that CKD is far more prevalent in the general population than previously appreciated, and latest reports indicate that as much as 16.8% of the US population may be affected.[2] It is also clear from these data that only a tiny minority of CKD patients ever advance to end-stage renal disease (ESRD), implying considerable heterogeneity in the risk of progressive renal function decline. As the Kidney Disease Outcomes Quality Initiative classification system is based on GFR alone, it affords no information regarding the relative risk of patients within each stage. There is thus an urgent need for a simple method of risk assessment that can be applied to all patients with CKD to identify those few at greatest risk.

PROTEINURIA: THE PRINCIPAL RENAL RISK FACTOR

The magnitude of proteinuria is widely recognized as a marker of the severity of glomerulopathy. A large body of evidence attests that proteinuria is also the single most important marker of prognosis in CKD. Population-based studies have identified proteinuria as a predictor of future decline in GFR[3] and the development of ESRD.[4] Even increases in albuminuria within the normal range have been associated with increased risk of subsequent overt proteinuria in subjects with type 2 diabetes.[5] Similarly, among subjects

with diabetic nephropathy[6,7] and nondiabetic CKD,[8–10] large prospective trials have confirmed baseline proteinuria as a strong independent predictor of the rate of GFR decline or ESRD. The importance of proteinuria as a risk factor is enhanced by the observation that both proteinuria and the associated risk of CKD progression may be modified by therapy. Several studies have reported that the relative reduction in proteinuria after initiation of renoprotective treatment and the level of achieved proteinuria are predictors of the subsequent rate of GFR decline.[7,10–12] The same has recently been shown to be true for microalbuminuria. Among 216 subjects with type 2 diabetes and microalbuminuria, a return to normoalbuminuria or a 50% reduction in albuminuria was associated with a significantly lower risk of a renal or cardiovascular event and a lower subsequent rate of GFR decline.[13] The benefit of minimizing proteinuria as a therapeutic goal has been confirmed by a prospective trial in which 360 subjects with nondiabetic CKD were randomized to treatment with a standard dose of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker versus the maximum antiproteinuric dose of either an ACEI or angiotensin receptor blocker (total of four randomized groups). For both treatments, subjects receiving the maximal antiproteinuric dose evidenced greater reductions in proteinuria (50–53% versus 35–41%) and a lower incidence of the primary end point of creatinine doubling, ESRD, or death (17.9 versus 31.3% ($P=0.025$) in the ACEI groups; 15.5 versus 29.5% ($P=0.022$) in the angiotensin receptor blocker groups) despite equivalent blood pressure control.[14] Moreover, proteinuria predicts whether or not patients will benefit from ACEI treatment. In one meta-analysis of data from 1860 subjects with nondiabetic CKD, ACEI treatment was associated with additional benefit versus other antihypertensives at all levels of risk among those with baseline proteinuria $\geqslant 0.5\,g\,day^{-1}$, but no additional renoprotection was observed if proteinuria was $<0.5\,g\,day^{-1}$.[15] The importance of proteinuria in defining renal risk has resulted in a proposal supported by the UK Consensus Conference on early stage CKD that the Kidney Disease Outcomes Quality Initiative classification system for CKD should be modified by the use of a suffix 'P' added to the stage to denote patients with significant proteinuria ($>1\,g\,day^{-1}$) and therefore at higher risk of progression.[16] The attraction of such an approach is that it is simple to apply and requires only a single test that already forms part of the routine investigation of patients with CKD.

OTHER RENAL RISK FACTORS

Despite the close correlation between the magnitude of proteinuria and renal outcomes, other factors have been also been identified as independent predictors of renal prognosis. Indeed, when subjects were subdivided according to whether or not they evidenced clinically significant proteinuria, substantial heterogeneity in risk was evident among subjects with proteinuria $\geqslant 0.5\,g\,day^{-1}$ and in those with $<0.5\,g\,day^{-1}$,[15] indicating that not all of the risk was attributable to proteinuria. A large number of independent risk factors for CKD or CKD progression has been identified and has been reviewed previously.[17] This apparently disparate list may conveniently be categorized into predisposing, initiating, and perpetuating factors (Table 1). Studies investigating these factors have provided valuable insights into the interaction between risk factors and mechanisms of CKD progression as well as suggesting novel targets for therapeutic intervention. One recent study has drawn attention to the important issue of competition between risks of ESRD and death, which becomes increasingly relevant in older patients such that among patients aged 65–84 years, the risk of ESRD exceeded the risk of death only when estimated GFR was <15 ml per min per $1.73\,m^2$.[18] Given the complex pathogenesis of CKD progression, it is not surprising, however, that each risk factor accounts for only a relatively small proportion of the total renal risk. This implies that a combined assessment of multiple risk factors is required to obtain a comprehensive assessment of risk. To make such an approach clinically applicable, it is necessary to identify a relatively small number of factors that together account for the majority of the variation in risk.

Table 1 | Risk factors for chronic kidney disease

Predisposing	Initiating	Perpetuating
	Primary renal disease	
	Urological disorders	
	Nephrotoxins	Nephrotoxins
Older age		
Gender		
Ethnicity		
Family history of CKD		
Metabolic syndrome		
Hyperfiltration states		
Low nephron number		↓Nephron number
Diabetes mellitus		
BP >125/75 mm Hg		SBP >130 mm Hg
Obesity		Obesity
High protein intake		High protein intake
Anemia		Anemia
↑Urinary albumin		Proteinuria
Dyslipidemia		Dyslipidemia
Cardiovascular disease		Cardiovascular disease
		Hyperuricemia
		Smoking
		Hypoproteinemia

RENAL RISK SCORES

Some efforts have already been made to combine renal risk factors into scoring systems that can be used to assess renal risk in individual patients. One approach has been to use decision-tree simulation and Bayesian modeling to assess risk and this has been applied to determine individual risk of ESRD in a hypothetical population of US patients using blood pressure and a measure of proteinuria as well as basic demographic data.[19] An alternative method is to employ multivariate analysis of baseline variables in longitudinal

cohort studies to identify independent predictors of renal outcomes and develop a risk score based on the coefficients of these variables. Among 1860 subjects with nondiabetic CKD from a combined database of 11 clinical trails, Cox proportional hazards analysis identified age, serum creatinine, proteinuria, and systolic blood pressure as independent risk factors for the combined endpoint of time to ESRD or creatinine doubling. A risk model was developed and used to stratify subjects into quartiles of risk. In the lowest risk quartile, the annual incidence of the combined end point was 0.4 versus 28.7% in the highest quartile for subjects in the control group and 0.2 versus 19.7% for those randomized to ACEI treatment.[15] Other studies have sought to develop risk scores for patients with specific renal pathologies. Using data from 1513 subjects with diabetic nephropathy included in the RENAAL study, multivariate analysis of baseline variables identified urine albumin/creatinine ratio, serum albumin, serum creatinine, and hemoglobin as independent risk factors for ESRD. Analysis of outcomes according to a risk score derived from the coefficients of these variables revealed a marked difference in risk between the first and last quartile (event rate 6.7 versus 257.2 per thousand patient years) (Figure 1). The importance of proteinuria was confirmed by the observation that albuminuria was the strongest single predictor of ESRD, but the risk score improved predictive power at least threefold, especially in low-risk subjects.[6] Similarly, multivariate analysis of data from 2269 patients with IgA nephropathy identified systolic blood pressure, proteinuria, serum total protein, serum creatinine, and histological grade at initial biopsy as predictors of time to ESRD. Age, gender, and severity of hematuria were then added to these variables to develop a scoring system for estimating 4- and 7-year cumulative incidence of ESRD. There was good agreement between estimated and observed risks (area under ROC curve 0.939; 95% CI, 0.930–0.964).[20]

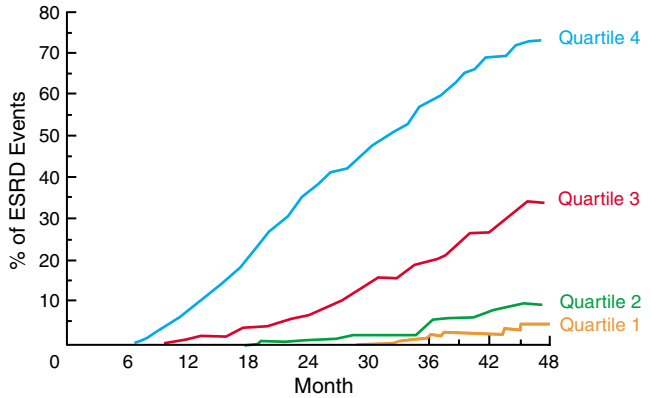

Figure 1 | Kaplan Meier curve showing the incidence of ESRD among patients with type 2 diabetes and diabetic nephropathy included in the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) Study, stratified into quartiles of a risk score derived from baseline serum creatinine, urine albumin/creatinine ratio, serum albumin, and hemoglobin.

FUTURE PROSPECTS

The studies discussed above demonstrate that it is feasible to define renal risk in individual patients using a small number of commonly assessed baseline variables. Each was performed in a distinct group of subjects with specific forms of CKD, yet there is remarkable similarity between the variables that entered the risk prediction models (Table 2). It seems likely that age, serum creatinine, a measure of proteinuria, systolic blood pressure, and serum albumin or total protein will be key variables in future risk scores. Validation of these risk scores in separate groups of patients is an important next step. To maximize the clinical applicability of renal risk scores, it would be desirable to develop a score that could be applied to a more general population of patients with all forms of CKD. It is likely that studies of such a patient group will identify other important predictors of risk that were not identified in the relatively homogeneous populations studied to date. For example, diabetes itself may emerge as a risk factor, but this could not have been identified in a study in which all patients had diabetes. It is also clear that the above methodology could readily be applied to the important additional task of defining cardiovascular risk in patients with CKD. Large epidemiological studies have drawn attention to the marked increase in cardiovascular morbidity and mortality associated with CKD, accounted for only in part by a high prevalence of traditional cardiovascular risk factors.[21] At present, it is not clear whether or not cardiovascular risk equations designed to predict outcomes in the general population are also applicable to those with CKD.

Table 2 | Summary of variables used to develop renal risk scores in different populations of subjects with CKD

Nondiabetic CKD (n=1860)[15]	Diabetic nephropathy (n=1513)[6]	IgA nephropathy (n=2269)[20]
1/serum creatinine HR 0.14 (0.11–0.18) for each 1-SD↑	*Serum creatinine (mg/dl)* HR 3.59 (2.90–4.45); χ^2=137.7	1/serum creatinine
24 h urinary protein (g/day) HR 1.10 (1.07–1.14)	log (UACR) HR 7.12 (4.7–10.8); χ^2=85.5	Proteinuria (dipstick)
Systolic blood pressure HR 1.14 (1.09–1.20) for each 10 mm Hg↑		Systolic blood pressure
	Serum albumin (mg/dl) HR 0.46 (0.34–0.62); χ^2=25.1 *Hemoglobin (mg/dl)* HR 0.90 (0.84–0.96); χ^2=10.6	Serum total protein
log (Age) HR 0.77 (0.68–0.86) for each 1-SD↑		Age
		Gender Histological grade Hematuria

HR, hazard ratio; UACR, urine albumin to creatinine ratio.

There is thus an opportunity to simultaneously develop both a renal risk score and a cardiovascular risk score applicable to CKD patients. Both are urgently required to facilitate targeted treatment of those at high risk, while avoiding unnecessary treatment and the attendant financial costs in low-risk patients.

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