Risk Stratification to Improve Care and Outcomes in Diabetic Kidney Disease

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About the Author

Dr. Navdeep Tangri, MD, PhD, is working on a clinical research program that is also translational, focusing on the improvement of clinical decision making for patients with advanced chronic kidney disease. He developed and validated the Kidney Failure Risk Equation (KFRE) to predict the need for dialysis in patients with chronic kidney disease, and is currently engaged in multiple validation and implementation exercises to increase the uptake of the KFRE.

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Introduction

Chronic kidney disease (CKD) is a global public health problem that affects one in eight Canadians, and nearly one in two with Type 2 diabetes (T2DM).[1-3] It is widely recognized as a potent risk factor for cardiovascular (CV) outcomes, all-cause mortality, and progression to kidney failure requiring dialysis or transplant.[4,5] End stage kidney disease is catastrophic for patients and families, but for most individuals who are identified as having high-risk CKD, progression is now preventable in this new era of guideline-directed medical therapy.[6-9]

This review will summarize a new paradigm for diagnosis, staging, and management of CKD, that is centered around risk of progression rather than kidney function (eGFR or serum creatinine alone).[8,9] We will describe the heterogeneity in the progression of kidney disease, as well as the clinical utility and usability of accurate risk prediction tools that can be used today in Canadian clinical practice.

CKD – Epidemiology and Variability in Risk of Progression

CKD is defined as loss of kidney function (eGFR < 60 mL/min/1.73m^2), or evidence of kidney damage (urine albumin to creatinine ratio > 3 mg/mmol) or imaging abnormalities), and a confirmation that these changes have been present for at least 3 months.[10] Longitudinal studies from healthy community-based populations suggest that most adults lose about 1 mL/min/1.73m^2 of kidney function after the age of 40.[11] In the general population, the prevalence of CKD is below 5% in younger adults (< 50 years of age), but rises to 35% in older adults (> 80 years of age).[12]

In adults with T2DM, the prevalence of CKD is much higher, and T2DM is the leading cause of kidney failure in Canada.[3,13] Studies from national health surveys in the United States indicate that 26% of adults with T2DM < 65 years of age had concomitant CKD, and this rose to 59% in those

older than 65.[14] In Canada, a study in primary care practices focusing on later stages of CKD (G3-G5) found an overall prevalence of 7.4% in the general population, but this rose to 27% in those with T2DM and hypertension.[1] These findings highlight the importance of screening with eGFR and urine ACR in all adults with diabetes (Type 1 and Type 2) on an annual basis.

It is important to note that while CKD is common, kidney failure requiring dialysis remains an uncommon event. Since 2018, there has been a plateau in the overall incidence in Canada, and 6,000 patients start dialysis or receive a transplant annually, at a rate of 200 per million persons.[15] Of these, approximately 3,000 are adults with T2DM, and more than 50% of new dialysis patients have T2DM as a cause of CKD or a comorbid condition.[15]

The gap in rates (140,000 per one million for prevalent CKD, and 766 per one million for incident dialysis) reflect the heterogeneity in disease progression, as well as the poor survival once patients reach renal replacement therapy.[15,16] It is likely that a minority of patients with CKD/diabetic kidney disease (DKD) are high-risk and drive the majority of kidney failure outcomes, while most patients progress slowly, and have competing CV events and do not ever reach kidney failure. As such, accurate risk stratification to identify these high-risk individuals early in the course of disease can be highly effective in preventing both kidney failure and CV events.[17]

Clinical Practice Guideline Recommendations

The Kidney Disease Improving Global Outcomes Guidelines (KDIGO) are the gold standard for guiding treatment for adults with CKD, and are typically endorsed by the Canadian nephrology community. The most recent update to the guidelines was released in March 2024, and acknowledges the importance of staging and risk prediction in determining optimal treatment for patients with CKD.

Staging for CKD requires testing for both eGFR and albuminuria, and patients are staged along a heatmap **(Figure 1)**. The heatmap represents relative

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.

Figure 1. KDIGO heatmap of increasing risk of developing CKD through decreasing glomerular filtration rate (GFR) and increasing and persistent albuminuria.[10]

risks for progression of kidney disease, CV events, acute kidney injury, and all-cause mortality.[10] While the heatmap represents a major advance over the eGFR-only staging system for CKD, there is considerable variation in absolute risk even within a single heatmap box. In fact, two individuals who are green or red can have up to an 80-fold variability in their risk of disease progression.[8] Therefore, risk prediction equations that estimate the absolute risk for each individual person are needed, available and recommended by the KDIGO clinical practice guidelines.

Risk Prediction Tools for Later Stages of CKD (G3-G5)

In adults with more advanced CKD (eGFR <60 mL/min/1.73m^2), the kidney failure risk equation (KFRE) is the most widely used and validated tool to predict CKD progression.[18] The equation was originally developed and validated in Canada (Ontario and British Columbia), and has subsequently been validated in more than 30 countries and two million individuals.[19] The KFRE is easy to calculate using freely available web sites (kidneyfailurerisk.com), electronic medical record integrations (Oscar Pro, Input Health), and through automatic reporting by medical laboratories (Alphalabs, Lifelabs) **(Figure 2)**.

In Ontario, Manitoba, and Alberta, the KFRE is used to determine the need for nephrology referral or interdisciplinary care, in combination with eGFR and urine ACR based criteria. Physicians who provide care for adults with CKD Stage G3+ should calculate the KFRE and can use it to guide referral to nephrology care as well as provide counselling for patients on their risk of dialysis. Studies comparing patient and provider perspectives on risk prediction have consistently shown that the KFRE is more accurate than nephrologists, and that patients value knowing their risk, as it improves their engagement and participation in shared decision-making.[20-23]

Risk Prediction Tools that Enable Early Intervention (G1-G3)

The treatment landscape for patients with CKD and DKD has changed dramatically in the last 10 years. From 2000-2015, patients with DKD were only treated with renin angiotensin aldosterone inhibitors (RAASi), and high-risk patients lost kidney function at 5-7 mL/min/1.73m^2/year even with optimal treatment. Since that time, landmark trials of SGLT2 inhibitor therapy,[24,25] followed by two large-randomized trials of finerenone, a nonsteroidal mineralocorticoid receptor antagonist (ns-MRA)[26] have shown that the progression of CKD can be reduced by up to 60% compared to RAASi therapy alone.[27] Furthermore, even high-risk patients can achieve a substantial reduction in eGFR slope to less than 3 mL/min/1.73m^2/year. Recently, top line data from the FLOW trial (semaglutide) was also released, confirming an additional 24% reduction in kidney disease progression and CV events in patients with DKD, further adding to the importance of a pillar-based approach for slowing CKD progression.[28]

In the current diagnostic and treatment paradigm, patients are unrecognized as having CKD until eGFR is typically <45 mL/min/1.73m^2, leading to a narrow window for intervention, and an increased risk of adverse effects and treatment discontinuation. Risk prediction tools that identify high-risk individuals for multi-drug therapy, early in the course of disease,

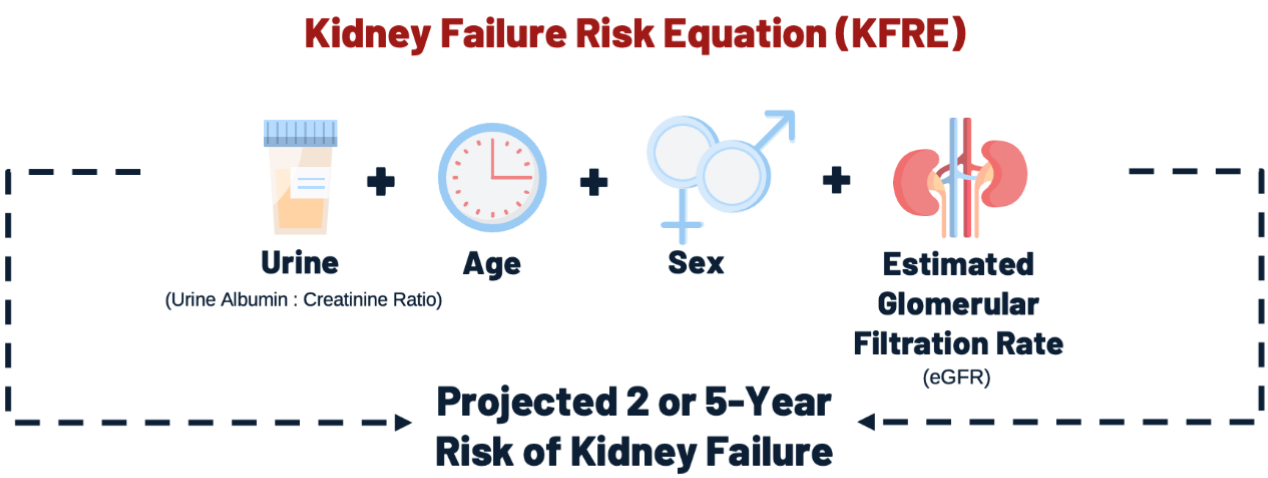

Figure 2. Summary of the key variables within the four- and eight-variable kidney failure risk equations.[18]

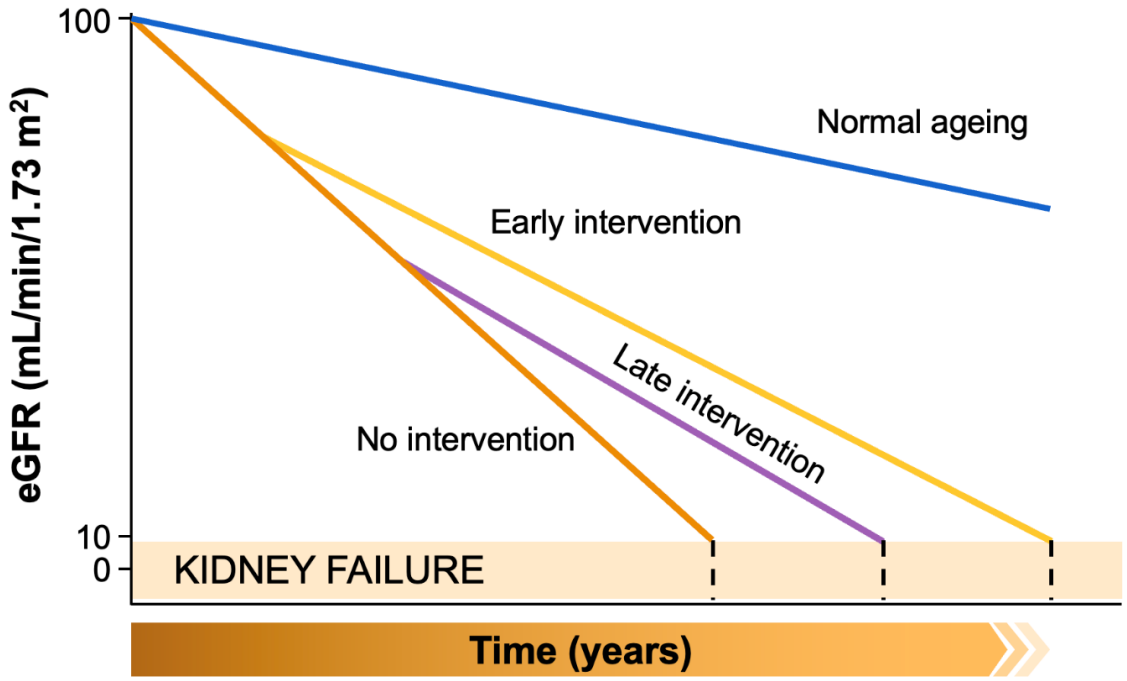

Figure 3. Display of the significant effect of early identification treatment onset for CKD; Adapted from Alexiuk & Tangri.[29]

when eGFR is preserved, can change how care is delivered **(Figure 3)**. These tools are now accurate and accessible, and have been rigorously validated in multiple countries and healthcare settings. In this section of the review, we will highlight two models that can be used to identify high-risk individuals with early stages of CKD.

CKD-PC eGFR Decline Model

The Chronic Kidney Disease Prognosis Consortium (CKD-PC) represents a group of multidisciplinary scientists who collaborate to develop and validate risk prediction tools for patients with CKD. In 2023, the CKD-PC investigators developed a new model to predict 40% decline in eGFR in patients with or without T2DM, and preserved kidney function.[8] These models, along with other CKD-PC models are available for use at www.ckdpcrisk.org

The CKD-PC models used rigorous methods and were developed and validated in 1.6 million individuals across 43 cohorts and 23 countries. The model uses routinely available data on demographics, laboratory variables, medications, and comorbid conditions to predict progression of kidney disease in adults with preserved eGFR. A list of the variables included in the models and the performance characteristics (AUC 0.77 in adults with T2DM) of these models are summarized in **Table 1**. It is important to note that these models are tied to actionable clinical thresholds and decisions. The authors recommend RAASi and SGLT2i therapy for patients at >1% risk of progression in 2-3 years, and multi-drug therapy for those at >5 % risk at 3 years.

Klinrisk Models

The Klinrisk models take a novel artificial intelligence/machine learning-based approach to risk prediction in patients with early stages of disease.[9] These models were developed in Canada and have subsequently been validated in multinational clinical trials, as well as in a recently presented study of 4.6 million U.S. adults with or without CKD at baseline. Similar to the CKD-PC models, the Klinrisk models are equally effective in adults with or without T2DM, and predict 40% decline in eGFR or kidney failure.

There are some important differences in the models and their implementation. The Klinrisk models are machine learning-based, and use laboratory data only, and therefore do not require information on comorbid conditions, medication or blood pressure. They are also highly accurate, with AUC ranging from 0.84-0.88 in development and external validation. In Canada, these models are available through Lifelabs Inc. as a patient paid test, and are accompanied by clinical decision support that aligns

	CKD-PC T2DM[8]	Klinrisk[9]
Variables	• Age (20-80 years) • Sex • eGFR • UACR • Systolic Blood Pressure • Antihypertensive Medication Use • Heart Failure • Coronary Heart Disease • Atrial Fibrillation • BMI • Smoking History • T2DM Medication • Hemoglobin HbA1c	• Age • Sex • eGFR • UACR • Random Glucose • Blood Urea (BUN) • Sodium • Potassium • ALT • Alkaline Phosphatase • Bilirubin • Albumin • ACR • Complete Blood Count • Calcium • Magnesium • Chloride • Phosphate • Bicarbonate
Population	N = 1.6 million from 43 cohorts, globally	N = 77,196 (study cohort) N = 4.6 million (validation)
Outcome	3-year probability of 40% decline in eGFR	2- and 5-year probability of 40% decline in eGFR
AUROC	0.77	0.84–0.88

Table 1. Summary of risk prediction models for early-stage CKD; courtesy of Navdeep Tangri, MD, PhD

with both KDIGO clinical practice guidelines and provincial criteria for referral to nephrology.

These models are therefore also actionable, and can be used in clinical practice today to facilitate early intervention in adults with T2DM.

Summary and Conclusions

CKD is common in patients with T2DM, but has a heterogeneous course. Risk prediction can transform the management of DKD by helping clinicians identify high-risk patients early when intervention is most effective. When high-risk patients receive guideline-directed medical therapy early, dialysis is entirely preventable. Our approach to DKD must include measurement of risk.

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