Findings and Implications of the REVEAL-CKD Study Investigating the Global Prevalence of Undiagnosed Stage G3 Chronic Kidney Disease

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Interview Summary

Chronic kidney disease (CKD) is a progressive condition that can lead to kidney failure and the requirement for renal dialysis or transplantation. Early-stage CKD is often missed because the disorder is initially asymptomatic; hence, many patients with CKD already have symptomatic advanced disease (Stages G4–G5) at the time of diagnosis. This is an important issue because the drugs available for the treatment of CKD are most effective when given during the early stages of the disease (Stages G1–G3). EMJ conducted interviews in July 2022 with two key opinion leaders, Navdeep Tangri from the University of Manitoba, Winnipeg, Canada, and Luca De Nicola from the University of Campania Luigi Vanvitell, Naples, Italy, both of whom have a wealth of experience in the management of patients with CKD. The experts provided important insights into the ongoing REVEAL-CKD study, which was designed to explore the global prevalence of undiagnosed Stage G3 CKD. This article describes the main findings of the REVEAL-CKD study published to date and their implications. Possible approaches to improving the diagnosis of CKD are also discussed.

INTRODUCTION

CKD is a progressive disorder associated with considerable morbidity and mortality. The global prevalence of CKD was 9.1% in 2017,[1] and the prevalence of the disease is predicted to increase during the next few years.[2] The severity of CKD is staged according to the glomerular filtration rate (GFR), which reflects renal function, and albuminuria, which reflects kidney damage. GFR is usually estimated using equations that consider serum creatinine level, age, sex, and/or race.[3] There are five estimated GFR (eGFR)-based stages of CKD and three albuminuria-based stages. Stage G1A1 (eGFR ≥90 mL/min/1.73 m^2 and no albuminuria) represents mild disease, and Stage G5 (eGFR <15 mL/min/1.73 m^2) denotes a patient who is approaching kidney failure.[3] Patients with end-stage kidney disease (ESKD) require renal replacement therapy or kidney transplantation; however, the 5-year survival and quality of life of most patients undergoing renal replacement therapy for ESKD is poor.[4] It is now recognised that CKD progression can be delayed if lifestyle modifications and pharmacological therapy are implemented early in the course of the disease.[3,5] However, CKD is asymptomatic during the initial stages and so is frequently diagnosed at an advanced stage, once symptoms have appeared.[6] REVEAL-CKD is a multinational, observational, longitudinal study designed to evaluate the prevalence of undiagnosed Stage G3 CKD in general populations across several countries, and to identify factors associated with undiagnosed Stage G3 CKD.[7] In this article, two nephrology experts, Tangri and De Nicola, discussed the importance of the REVEAL-CKD study and the implications of the results that have been published to date. Both key opinion leaders highlighted the consistently high rate of undiagnosed Stage G3 CKD in all countries included in the study, and emphasised the need to improve the early detection of CKD so that treatments can be initiated to delay disease progression and prevent the need for dialysis.

WHY THE EARLY DETECTION OF CHRONIC KIDNEY DISEASE IS IMPORTANT

De Nicola explained that the management options for CKD have expanded during the past 30 years, and that the availability of new treatments developed recently has increased the importance of diagnosing CKD at an early stage. He noted that 30 years ago, nephrologists were focused on kidney dialysis as the main treatment method because medical therapies were considered ineffective even for moderate degrees of CKD (defined by serum creatinine levels in the range of 1.5–2.0 mg/dL). De Nicola stated: "Dialysis was the greatest innovation in nephrology at that time." However, De Nicola went on to say that although renal replacement therapy remains a life-saving treatment, it is now recognised that advances in dialysis have plateaued and, at present, it remains a therapy with limited effects on the long-term survival and quality of life of patients. In fact, he highlighted that the mortality rate for patients on dialysis has not changed in the last 15–20 years. According to De Nicola, the major focus of CKD treatment has now shifted from substitution of renal function (for example, with haemodialysis or peritoneal dialysis) to preservation of renal function through the use of multifactorial (conservative) therapy that aims to prevent not only ESKD but also cardiovascular events, which are major complications of CKD. He stressed that the "mission of every nephrologist should be to avoid dialysis" in their patients. De Nicola mentioned antiproteinuric intervention as the key component of multifactorial therapy to improve long-term kidney survival, and emphasised that these treatments show the greatest potential to slow the progression of CKD to ESKD when initiated at an early stage.

Tangri noted that CKD is asymptomatic during the initial stages and that symptoms only occur once more than 70% of kidney function has been lost, at which point the window to intervene is closed or closing rapidly. Tangri explained that diagnosis of CKD at Stages G1–G3, and ideally at Stages G1–G2, with albuminuria as the diagnostic test, allows the implementation of therapies that have the potential to avoid the need for dialysis. Tangri noted that diagnosing and treating CKD at Stage G4 of the disease can only delay the time to kidney replacement therapy, and is too late to prevent a lifetime of dialysis.

MEDICAL THERAPIES THAT ARE AVAILABLE FOR CHRONIC KIDNEY DISEASE

Tangri considered a renin-angiotensin-aldosterone system inhibitor (angiotensin converting enzyme inhibitor or angiotensin receptor blocker) and a sodium-glucose co-transporter-2 inhibitor as foundational therapy for CKD, and noted that most patients with CKD benefit from these drugs. He also indicated that patients with diabetes and Stage G1–G3 CKD may additionally benefit from finerenone, a non-steroidal mineralocorticoid receptor antagonist. The same pharmacological agents were described by De Nicola, who also mentioned that anti-endothelin drugs were being investigated as potential new therapeutic options for CKD. Tangri emphasised the importance of controlling blood pressure and blood glucose levels in patients with CKD.

According to Tangri, CKD progression and cardiovascular disease are the two main contributors to healthcare costs in patients with CKD. Since the drugs available for the treatment of CKD both slow disease progression and reduce the incidence of cardiovascular events, Tangri argued that timely diagnosis and intervention would not only directly benefit the health of the patient, but also reduce treatment costs for health systems and payers.

GUIDELINES FOR THE SCREENING AND DIAGNOSIS OF CHRONIC KIDNEY DISEASE

De Nicola stated that, in his view, the most comprehensive position paper considering these aspects is the consensus established at the recent Kidney Disease: Improving Global Outcomes (KDIGO) conference on 'Early Identification and Intervention in CKD', the findings of which were published in 2021.[5] Tangri also referred to the KDIGO recommendations[3,5] and mentioned the National Institute for Health and Care Excellence (NICE) guideline available in the UK.[8]

WHY ARE DIAGNOSES MISSED IN PATIENTS WITH STAGE G3 CHRONIC KIDNEY DISEASE?

According to both experts, the major reason for missed diagnoses is that early-stage CKD is asymptomatic, or manifests only with subtle symptoms. De Nicola also suggested that a lack of awareness of CKD among primary care physicians, and consequently among their patients, contributes to a diagnosis not being made. In the opinion of Tangri, CKD has been viewed for many years as a complication of diabetes and hypertension rather than as a standalone entity, because management strategies were focused on the 'underlying' diseases. He continued that although the relevant guidelines are understood by the nephrology community, these have not been well disseminated among primary care physicians, who have the challenge of being aware of and implementing many different guidelines for various medical conditions.

THE REVEAL-CKD STUDY

REVEAL-CKD is a real-world, multinational, observational study designed to evaluate the prevalence of, and factors associated with, undiagnosed Stage G3 CKD in general populations from several countries.[7] Tangri is the principal investigator of the REVEAL-CKD study, and contributed to the design of its protocol. De Nicola is on the steering committee of the REVEAL-CKD study, and became involved in the project because his main field of research is the conservative therapy of CKD.

Tangri explained that the primary purpose of REVEAL-CKD was to "shine a spotlight" on how often CKD is undiagnosed by looking at the gap between claim-based diagnoses, when CKD is coded in the medical records, and laboratory-based 'gold standard' diagnoses based on eGFR. De Nicola elaborated that REVEAL-CKD was designed to estimate the prevalence of undiagnosed Stage G3 CKD by identifying patients with at least two eGFR levels, recorded at an interval of at least 3 months, that are indicative of Stage G3 CKD (≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2), and then verifying whether these patients did receive a diagnosis of CKD according to a standard International

Classification of Diseases 9/10 diagnosis code for CKD in the medical records. Tangri added that the study would also explore whether coding the disease in medical records affected disease management, including the prescribing of disease-modifying treatments and the attainment of blood pressure control and glycaemic control targets. Both experts emphasised that REVEAL-CKD is the largest multinational study to address the important issue of CKD underdiagnosis. Tangri highlighted the global context as a unique advantage of REVEAL-CKD, with the same statistical protocol and analysis used consistently in different settings to identify global health problems that are not limited to a single country.

Findings of the REVEAL-CKD Study Published to Date

Results from the REVEAL-CKD study for patients in France, Germany, Italy, Japan, and the USA have been presented at several major scientific meetings and published in the form of abstracts.[9-13] De Nicola explained that the main finding in Italy, obtained using databases from 900 Italian general practitioners that included over 1.2 million patients, was that 77% of patients with proven Stage G3 CKD were undiagnosed by their general practitioners. The published data indicate that the rate of undiagnosed Stage G3 CKD reported for Italy was broadly consistent with that observed in France (94%), Germany (74%–84%), Japan (87%), and the USA (62%).[9-13]

Both experts highlighted the finding that the rate of undiagnosed Stage G3 CKD was higher in older patients, females, and those with Stage G3a CKD (GFR ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2) versus those with Stage G3b CKD (GFR ≥30 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2). Tangri speculated that the higher rate of undiagnosed CKD in older adults might reflect a "fatalistic view" of CKD as a consequence of ageing, rather than as a disease in its own right. He also suggested that the higher rate of undiagnosed CKD in females may be related to how GFR is estimated, with some physicians focusing on the serum creatinine value, which is lower in females than males because of less muscle mass, rather than on a slightly lowered eGFR, which accounts for body size. Given the above, Tangri noted that older females with Stage G3 CKD may be particularly disadvantaged in regard to timely diagnosis, and thus might be less likely to receive optimal treatment.

Both experts pointed out that the rate of undiagnosed Stage G3 CKD was almost as high in patients with known risk factors for CKD, such as diabetes, heart failure, or hypertension, as in patients without any of these risk factors. De Nicola explained that this finding was unexpected because it is well known among clinicians that patients with these comorbidities are at an increased risk of developing renal dysfunction, and hence need to be tested for CKD. Both experts agreed that this finding may be related to the perception among many physicians that CKD is a consequence or complication of a comorbidity rather than a disease in its own right, and both experts concurred that this mindset must be changed to improve the diagnosis of early-stage CKD. Another possibility raised by Tangri was that a physician may not feel the need to code for CKD in a patient being treated for hypertension with a renin-angiotensin-aldosterone system inhibitor because the patient is already receiving an appropriate therapy for CKD. However, Tangri added that failing to code for CKD in the medical record may mean that the patient is less likely to receive one of the newer agents available for CKD, or any treatment developed in the future.

Tangri also commented on why patients who were undiagnosed for CKD at the index date were unlikely to receive a later diagnosis. He suggested that the low rate of subsequent diagnosis may reflect the "reluctance" of some physicians to diagnose CKD, perhaps because they view CKD as a complication of other diseases. Tangri speculated that the minority of patients who did receive a subsequent diagnosis of CKD may have had declining eGFR values rather than relatively stable levels during the follow-up period, which prompted the physician to code for CKD.

Tangri confirmed that the REVEAL-CKD study is ongoing. He explained that the next phase of REVEAL-CKD is crucial because it will evaluate whether recording a diagnosis of CKD makes it more likely that the appropriate targeted treatment is given. Tangri also stated that the study will investigate the link between undiagnosed CKD and outcomes, although this analysis will be more exploratory because

outcomes are related to factors other than treatment, such as patient-related, social, and economic factors. It is expected that the findings will be published in waves, with an initial publication in the next few months, followed by a series of additional papers.

Implications of the REVEAL-CKD Study Findings and Calls to Action

Both experts proposed actions that healthcare professionals and others should consider taking, based on the findings of the REVEAL-CKD study published to date. De Nicola emphasised that non-nephrologists, especially primary care physicians but also specialists such as cardiologists and diabetologists, need to receive straightforward and easy-to-follow guidance on CKD diagnosis and management. This guidance should focus on three critical points: who to screen (those with risk factors for CKD such as diabetes, hypertension, heart failure, obesity, and older age); how to screen (serum creatinine measurement and urinalysis for proteinuria); and when to refer a patient to a nephrologist (Stage G3b or worse CKD [<45 mL/min/1.73 m^2], or albuminuria at any stage). Tangri agreed that all patients with diabetes or hypertension should be screened for albuminuria as an indicator of CKD. He also highlighted other groups that might benefit from screening, including anyone with a family history of kidney failure (i.e., renal dialysis or transplantation) and people in high-risk geographical locations or ethnic communities (e.g., the First Nations community in Canada, South Asian communities in the UK, and agricultural communities in the developing world).

In the opinion of De Nicola, better communication is needed to make healthcare professionals, patients, and the public more aware of the therapies available for CKD so that there is a shift in the perception of CKD from an 'untreatable' to a 'treatable' disease. De Nicola argued that the focus of patient organisations should encompass not only the interests of patients needing dialysis or kidney transplantation, but also those of the larger population of patients with non-dialysis-dependent CKD, since this will promote the implementation of preventive strategies that slow the progression of CKD to ESKD. De Nicola suggested that the involvement of patient organisations and the public would help to influence decision-makers at health institutions, and thereby alter healthcare policies to improve the early detection of CKD. He added that input from patients will require publicity in the media, including radio, television, and social media networks, to promote CKD awareness.

Similarly, Tangri's call to action was to improve the recognition of CKD among primary care physicians as a standalone disease with its own specific therapies, as this would lead to a change in mindset in how the disease is viewed. He stated that achieving this goal will need a multiple-prompt approach, including journal articles, presentations, and social media messaging, because healthcare professionals vary in their resource and knowledge-sourcing preferences. Tangri also advocated distilling guidelines down to actionable messages and recommendations aimed at primary care providers, since he considered CKD to be a 'primary care disease'. In addition, Tangri mentioned that disease-specific foundations and charities can play a significant role in distributing evidence-based information to the public.

Tangri argued that improving workflow automation would be of help to busy primary care physicians who deal with the diagnosis and management of a wide range of health conditions, each with their own guidelines. He proposed that the diagnosis of CKD should be automatically entered in the electronic health record if the gold standard diagnostic criterion is met (i.e., two abnormal GFR measurements more than 90 days apart), with the physician retaining the autonomy to remove the diagnosis if it was subsequently concluded that CKD was not the underlying cause. Tangri also suggested the introduction of a prompt in the medical record for eligible patients who had not received a screening test for CKD, since this might help primary care physicians to implement evidence-based recommendations. He emphasised that automation and workflow assistance represent an unmet opportunity to improve CKD screening in patients who meet the appropriate criteria, but he also highlighted the challenge of electronic health record providers implementing necessary changes to such systems.

FUTURE PROSPECTS AND CONCLUSIONS

De Nicola concluded that efforts are needed to change the mindset of clinicians, and especially primary care physicians, so that they perceive CKD as a standalone, treatable disease. He stressed that patient organisations could play a role in driving changes in healthcare policy to improve the diagnosis of CKD, because the "value and efficacy of negotiations and communication definitely improve when the 'voices' of patients are involved."

Tangri concluded that primary care physicians need to be made aware of the importance of diagnosing CKD, stating: "Diagnosis matters because you are more likely to treat better." He proposed that the dissemination of straightforward recommendations for CKD diagnosis and treatment, and the automation of workflow, may improve the diagnosis of early-stage CKD, and hence patient outcomes in the future.

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