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Recent International Progress in Preventive Nephrology and the Road Less Traveled Ahead

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Implementation of clinical practice guidelines for chronic kidney disease (CKD) is of great importance for all clinicians who care for the affected patients.[1–4] On a population level, the primary care setting is broadest, but nephrology services are more likely to be offered for the subpopulation with advanced kidney diseases. There is considerable room for improvement in the care of individuals with CKD by primary care clinicians and nephrologists alike as assessed by the international Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of CKD.[5] This CKD outcomes and practice patterns study (CKDopps) shows poor implementation of 1 recommendation for laboratory monitoring and 4 interventions that slow CKD progression from the KDIGO guideline in the nephrology practice prospective cohorts of Brazil, France, Germany, and USA, using clinical data for the CKD population (n = 7204) treated between 2013 and 2017.[6] The findings are mostly confirmatory, but are novel and important, particularly in their relative consistency, with a few exceptions, for suboptimal clinical practice guideline implementation in nephrology from these 4 countries on 3 continents. Nephrology clinics were stratified by geographic region within each country and clinic characteristics (size and public vs. private) using inclusion criteria of all eligible patients ≥18 years of age with an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2 and no history of dialysis or transplant.[6] Population characteristics (Table 2 of the study) included mean age >65 years in all counties, some variability in the causes of CKD, ≥96% prevalence of hypertension, and mean eGFR ranging from 25.7 ± 11.6 ml/min per 1.73 m^2 in Brazil to 32.2 ± 11.3 ml/min per 1.73 m^2 in France. Polypharmacy was universal, with the mean number of medications ranging from 7 in Brazil to 11 in the USA.

Albuminuria is one of the key elements of the KDIGO cause–GFR–albuminuria CKD definition and classification system that conceptually illustrates the risk stratification using the familiar heat map diagram for the laboratory tests.[1] Albuminuria or proteinuria was routinely measured in fewer than half of the patients in Brazil (36%), Germany (36%), and the USA (42%), but the 89% measurement in France is attributed to health authority recommendation for albuminuria testing as part of a panel for an annual CKD monitoring with 100% reimbursement. The testing showed the overall prevalence of CKD stage A3 varied from 36% to 48% in Brazil and the USA, respectively, with a higher prevalence in the diabetes population, as anticipated. Low or absent testing for albuminuria or proteinuria is a common finding in population studies of CKD[7] and randomized trials in cardiovascular disease, yet one would expect nephrology practices to perform better. The investigators speculate that the French protocol for urine testing is not generalizable, which may be true contextually for the specific approach. However, nationally implemented protocols with reimbursement incentives are likely to succeed in any country in which the design is tailored to the clinician workflow.

Hypertension control revealed mean systolic blood pressure ranged from 133 ± 21 to 142 ± 20 mm Hg. Albuminuria was predictive of higher systolic blood pressure, but the albuminuria severity did not correlate with increased angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, which was was 67%, 78%, 81%, and 52%, in Brazil,

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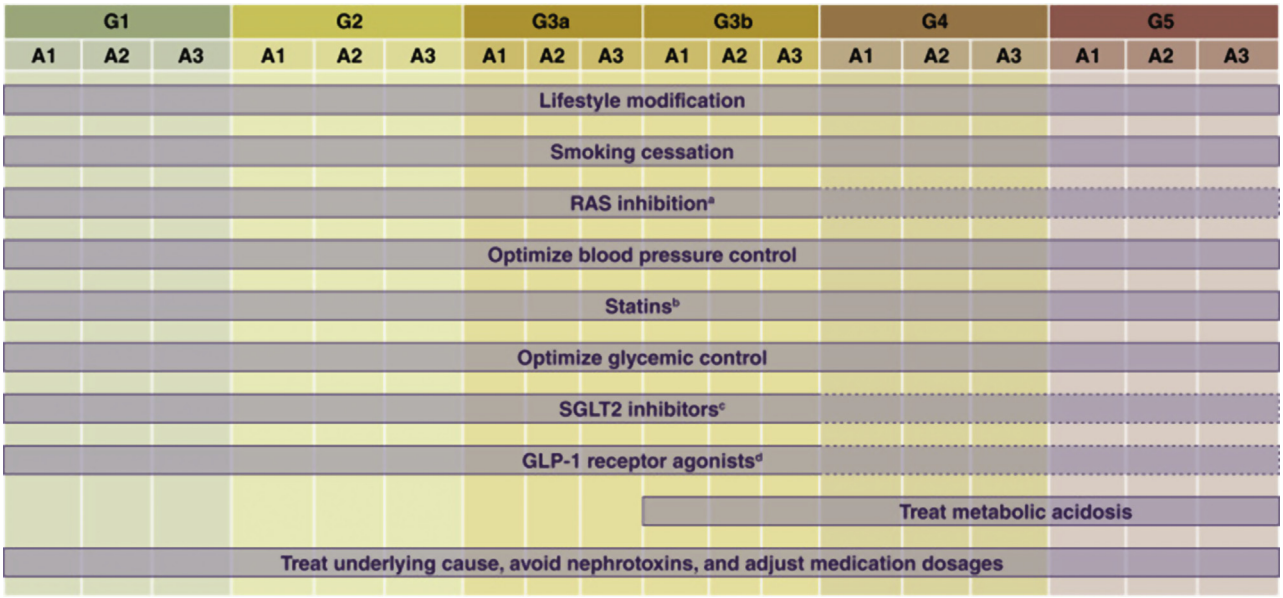

Figure 1. Interventions to slow CKD progression and/or reduce cardiovascular risk. [a]Unclear if and when to discontinue RAS inhibition in advanced CKD. [b]Statins should not be initiated for those beginning dialysis therapy. However, patients already receiving statins at the time of dialysis initiation can continue their statin treatment. [c]Applies to CKD patients with type 2 diabetes only. SGLT2 inhibitor is recommended as first-line treatment with metformin and may also have benefits in those with CKD and no diabetes. SGLT2 inhibitors should be initiated if eGFR is 30 ml/min per 1.73 m^2 and can be continued through G4–G5 until initiation of dialysis, at which point the SGLT2 inhibitor should be discontinued. There is no evidence for initiation of SGLT2 inhibitors if eGFR <30 ml/min per 1.73 m^2. [d]Applies to CKD patients with type 2 diabetes only. GLP-1 receptor agonist can be considered when SGLT2 inhibitor and/or metformin is not tolerated or glycemic target is not reached. Dulaglutide can be used if eGFR is >15 ml/min per 1.73 m^2; exenatide can be used if creatinine clearance is >30 ml/min; there are limited data for use of liraglutide, lixisenatide, or semaglutide in severe CKD. Consult dosing recommendations for use of these agents in CKD G4 and G5. CKD, chronic kidney disease; estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; RAS, renin–angiotensin system; SGLT2, sodium-glucose cotransporter-2. Reproduced with permission from Shlipak *et al.*[9]

France, Germany, and the USA, respectively. The authors address the contraindications and controversies regarding angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use at low eGFR. The clinician survey shows that a minority of nephrologists in all 4 countries reported a target blood pressure of <130/80 mm Hg, as currently recommended, although the contemporary relevance to this is challenging to interpret in the context of the changes in the blood pressure target during the study period.

Diabetes was a leading cause of CKD ascertained by nephrology assessment or by kidney biopsy and a major comorbidity. Overall, mean glycemic control was close to the target glycated hemoglobin level of ~7% (53 mmol/mol). Relatively new kidney and cardioprotective type 2 diabetes medications were not assessed. Lifestyle modifications, as captured by patient survey, were poorly implemented in the countries assessed, except for relatively high reporting of dietary sodium restriction education and low active smoking prevalence varying from 5% in Germany to 12% in France. Poor implementation of lifestyle recommendations does little to address the remarkable prevalence of obesity, defined as ≥30 kg/m^2 in 33% of Brazil, 36% of France, 40% of Germany, and 52% of the USA.

One major limitation not addressed by the investigators is the missing data for patients with advanced CKD who are outside of nephrology care in each of the countries. Surveillance data from the USA consistently show about one third of patients who initiate dialysis received little or no nephrology services in the previous year, a figure that has not changed significantly over the past decade.[7] A recent large French study showed that emergency dialysis starts comprised about 30% of incident patients (2681 of 8856), a finding that was strongly associated with inconsistent nephrology service patterns.[8]

Several guideline implementation variables in nephrology practice are not studied that may be further assessed by future CKDopps studies or other investigations, including vintage following the guideline publication, evidence level, national health policy and reimbursement influence, and, most of all, associations with hard outcomes. How has adherence to guideline statements changed over the consecutive years following publication in

January 2013? The available data from the current study are probably inadequate to allow for meaningful chronological assessment. Table 1 of the study shows the grading of recommendations, assessment, development, and evaluations (GRADE) system level for each statement assessed, varying from 1A (recommend—high) to 2D (suggest—very low). What is the association between adherence to the statements stratified by the GRADE level? National health policies play an obvious role in the results. Guidelines from the USA endorsed the KDIGO CKD guideline,[2] whereas those in France were different.[8] For example, nephrology consultation indications from France national guidelines are for eGFR <45 ml/min per 1.73 m^2 in contrast to KDIGO's <30 ml/min per 1.73 m^2 that resulted in both higher mean eGFR and a greater proportion of the population with eGFR of 30 to 60 ml/min per 1.73 m^2 in France (54%) versus the 3 other countries evaluated. Reimbursement policies in France impacted increased urine testing, as noted previously. What will be the impact of the U.S. Advancing American Kidney Health Initiative's Kidney Care First and Comprehensive Kidney Care Contracting payment models for CKD G4–G5 on nephrology practice? What will be the impact of Health-care Effectiveness Data and Information Set annual albuminuria and eGFR testing among the diabetic population downstream in USA nephrology? Most importantly, to what degree does real-world adherence to CKD guideline progression interventions result in attenuated loss of eGFR? How will the more recent CKD progression interventions, alkali therapy for CKD metabolic acidosis and sodium glucose cotransporter-2 inhibitor use, be implemented?

Risk stratification should inform data-driven allocation of limited nephrology services in all countries. An updated diagram of interventions to slow CKD progression and reduce cardiovascular risk by CKD stage was recently published by KDIGO (Figure 1).[9] Health policy and reimbursement incentives as well as nationally organized protocols are attractive implementation tools, as suggested by the French experience, and will be assessed further in the US payment models. Preventive nephrology is becoming an exciting reality based on the interventions assessed by CKDopps and emerging therapies. Kidney health professionals can transform a therapeutic focus primarily on replacing kidney failure to one that also realistically avoids or delays kidney failure.

DISCLOSURE

JAV reports consulting fees from the CKD Advisory Board of RenalytixAI, plc.

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