Editorial

World Kidney Day 2020: Advances in Preventive Nephrology

Jia Liang Kwek,[1] *MBBS, FAMS, MRCP*, Terence YS Kee, [1] *MBBS, FAMS, FRCP*

Current international guidelines define chronic kidney disease (CKD) as decreased kidney function shown by glomerular filtration rate (GFR) of >60 mL/min per 1·73 m^2 and/or presence of markers of kidney damage for >3 months.[1] CKD patients are at risk of progression to end-stage kidney disease (ESKD), cardiovascular events and mortality.[2] Global CKD prevalence is high, ranging from 11–13%.[3] Globally, CKD-related death has increased by 28.8% from 2006 to 2016, resulting in 1.19 million deaths in 2016.[4]

In Singapore, the prevalence of CKD was reported to be 15.6% in 2007;[5] the prevalence of CKD in the diabetes population was even higher at 53%.[6] CKD prevalence is projected to increase to 24.3% by 2035 due to the rising incidence of diabetes mellitus, hypertension, higher detection rate and an ageing population.[7] CKD-related deaths in Singapore increased from 380 in 2016 to 638 in 2018, the 6th most common cause of death in Singapore.[8] The number of patients initiated on dialysis has increased from 901 (age-standardised rate [ASR] 190.4 per 1,000,000 population) in 2008 to 1300 (ASR 194.9 per 1,000,000 population) in 2017.[9] The most common causes of ESKD among incident dialysis patients in 2017 were diabetes mellitus (67.1%) and chronic glomerulonephritis (14.6%).[9]

CKD is a major public health problem in Singapore and it is timely that this year's theme for World Kidney Day focuses on the importance of preventive intervention to avert the onset and progression of kidney disease. Preventive interventions can occur at 3 levels: 1) primary prevention is introduced to prevent occurrence of CKD; 2) secondary prevention is introduced to reduce impact of CKD through earlier diagnosis and prompt treatment of early CKD; and 3) tertiary prevention is introduced to soften the impact of CKD by helping patients manage the complexity of CKD. This is the framework that the healthcare community in Singapore has adopted to combat the CKD epidemic.

Primary Prevention

Control of modifiable risk factors of CKD, especially diabetes mellitus and hypertension, remains the cornerstone in primary prevention of CKD. Diabetes mellitus is the most common cause of CKD in Singapore and the proportion of incident dialysis patients with diabetic kidney disease (DKD) has increased from 45.9% in 1999 to 67.1% in 2017.[9] In 2016, the Ministry of Health of Singapore announced that it had declared War on Diabetes since if nothing was done to prevent diabetes, the number of Singaporeans living with diabetes was projected to reach 1 million by 2050.[10] This initiative signified government leadership and support in preventing and managing diabetes in Singapore. The War on Diabetes was fought on several fronts in schools, supermarkets, food and beverage sector and local food industry to ensure the availability of healthier food choices to Singaporeans, as well as through large-scale programmes and collaborations with public agencies like Sport Singapore, People's Association and National Parks Board to increase accessibility of Singaporeans to physical activity. A national primary preventive programme against diabetes was a critical component in the primary prevention of CKD through the reduction of DKD incidence.

Strict control of glycaemia and blood pressure and the use use of renin-angiotensin system (RAS) blockade, sodium-glucose cotransporter 2 (SGLT-2) inhibitor and Dietary Approaches to Stop Hypertension diet have been shown to be beneficial in the primary prevention of CKD. The onset of persistent albuminuria (an early indication of CKD in at-risk populations) is commonly used as a primary outcome measure in CKD prevention studies. In a Cochrane review by Ruospo et al, strict glycaemic control (HbA1c <7%) was associated with a small clinical benefit in onset of albuminuria in diabetic patients, even though the long-term benefit of strict glycaemic control was uncertain.[11] In the population-based Atherosclerosis Risk in Communities

[1]Department of Renal Medicine, Singapore General Hospital, Singapore
Address for Correspondence: A/Prof Terence Kee Yi Shern, Renal Medicine Office, Level 3, The Academia, 20 College Road, Singapore 169856.
Email: terence.kee.y.s@singhealth.com.sg

Study, modest population-wide reductions in systolic blood pressure (SBP) were associated with fewer incident CKD events.[12] Both Bergamo Nephrologic Diabetes Complications Trial and Randomised Olmesartan and Diabetes Microalbuminuria Prevention Study found that the use of RAS blockade delayed onset of albuminuria in diabetic non-albuminuric patients.[13,14] In the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial, the use of SGLT-2 inhibitor was associated with lower rate of incident nephropathy.[15] A systemic review by Tahavi et al found that adherence to DASH diet was inversely associated with risk of CKD.[16]

Secondary Prevention

Patients are asymptomatic in the early stages of CKD. Hence, primary healthcare plays an essential role in secondary prevention of CKD by screening at-risk populations to diagnose early CKD. A systemic review by Komenda et al suggested that it was cost-effective to screen for CKD in patients with diabetes mellitus and hypertension.[17] Currently, primary healthcare doctors perform regular screening of renal panel and urine albumin to creatinine ratio in patients with hypertension and/or diabetes mellitus. In Singapore, a structured programme called Nephrology Evaluation, Management and Optimisation (NEMO) was launched by the National University Hospital and National Healthcare Group Polyclinics (NHGP) with support from the Ministry of Health to manage patients with DKD in NHGP. It commenced in April 2011 to evaluate patients with diabetes mellitus for DKD, optimise RAS blockade and DKD management and monitor its progression. In November 2013, NEMO reported an improvement or resolution of albuminuria in 40% of patients who completed the programme.[18]

In April 2017, the Holistic Approach in Lowering and Tracking CKD (HALT-CKD) programme was launched by the Ministry of Health. It was an expansion and extension of the NEMO programme and included all CKD patients in Singapore. It is an ongoing programme that aims to: 1) recruit and track all CKD stage 1–4 patients of any cause in every polyclinic; 2) slow down CKD progression with control of risk factors and RAS blockade in all CKD stages; and 3) encourage shared-care collaboration between primary healthcare and hospital renal physicians at CKD stage 3B–4. Accurate diagnosis and early initiation of treatment of underlying CKD cause, institution of RAS blockade, control of blood pressure and diabetes, avoidance of nephrotoxic agents, dietary (avoidance of high-protein diet >1.3 g/kg/day) and low salt intake (sodium <90 mmol or <2 g/day) and lifestyle modifications are some of the key aspects of slowing down CKD progression.[1] However, not all CKD patients are able to achieve these targets. For example, Teo et al reported that the mean protein intake of most CKD patients exceeded the recommended guidelines in a Singapore cohort.[19] Hence, one of the aims of HALT-CKD is to achieve and track the attainment of some of these measures in CKD patients in the polyclinics. Strong collaboration between primary healthcare physicians, hospital renal physicians and allied healthcare groups are needed to guide and educate CKD patients to achieve these aims.

After RAS blockade, the discovery of SGLT-2 inhibitor has shown great promise in slowing down CKD progression in recent trials. In the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial, SGLT-2 inhibitor demonstrated a lower risk of 30% of a composite endpoint (ESKD, doubling of serum creatinine level or death from renal or cardiovascular causes) in proteinuric diabetic patients who were already on RAS blockade at a median follow-up of 2.62 years.[20] Further studies are being conducted to examine SGLT-2 inhibitor effect on a wider range of GFR and non-diabetic CKD population.[21–3]

Treatment of the underlying cause of CKD is an important component in the secondary prevention of CKD, especially in patients with chronic glomerulonephritis. There has been much progress made in the management of chronic glomerulonephritis. The Kidney Disease: Improving Global Outcomes initiative organised a Controversies Conference on glomerular diseases in November 2017 with updates on the pathogenesis, workup and therapies for glomerulonephritis.[24,25] Such efforts will help to improve the outcomes of CKD patients with glomerulonephritis. More findings on potential biomarkers and therapies for the whole spectrum of glomerulonephritis are expected in the future.

Tertiary Prevention

Adverse clinical outcomes including ESKD, all-cause mortality and cardiovascular events are important considerations in management of CKD patients. Lower GFR and albuminuria are associated with worse cardiovascular outcomes, mortality and risk of ESKD.[26, 27] To lower the risk of adverse clinical outcomes, tertiary prevention of CKD involves continuation of CKD retardation measures and management of modifiable cardiovascular risk factors

and CKD complications. Accurate prediction of adverse clinical outcomes has gained much attention in recent years. With accurate prediction, more effort and focus can be given to the most susceptible CKD groups to improve their outcomes; timely education can also be provided to groups who have a high risk of progression to allow sufficient time to engage them on their long-term kidney care plans.

Tangri et al have proposed and validated a kidney failure risk equation (KFRE) model for progression of CKD to ESKD in a Canadian population and subsequently validated it in multinational cohorts.[28,29] Wang et al validated and recalibrated KFRE for improved performance in a Singapore cohort, although they did not have a validation dataset to confirm the improved performance of the recalibrated KFRE compared to the original KFRE model.[30] Grams et al proposed and validated a risk prediction model for the probability and timing of kidney failure that required kidney replacement therapy, non-fatal, non-fatal cardiovascular event and death from 29 cohorts in 30 countries.[31]

Blood pressure control and target in CKD population is widely discussed and investigated. For cardiovascular outcomes, the landmark Systolic Blood Pressure Intervention Trial (SPRINT) compared SBP <120 mmHg and <140 mmHg in a non-diabetic cohort, which included a CKD subgroup. The study demonstrated that patients with SBP <120 mmHg had better primary cardiovascular outcome (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.64–0.89) and all-cause death (HR 0.73, 95% CI 0.60–0.90).[32] It is to be noted that SPRINT measured SBP with automated devices (5-minute wait period and mean of 3 readings) and often in the absence of observers, which may result in readings that were lower than typical office blood pressure readings. This cardiovascular benefit for intensive blood pressure control is, however, less certain in diabetic and elderly CKD populations due to limitations in the design of study trials.[33,34] The effect of intensive blood pressure control in reducing ESKD risk is also less certain, but there is suggestion that intensive blood pressure control can protect CKD population against ESKD risk, especially in proteinuric CKD.[35]

Moving Forward

Research in CKD has advanced significantly in recent years. Apart from clinical parameters (GFR and proteinuria), more biomarkers that relate to the pathogenesis of CKD are needed to better predict CKD progression and develop targeted therapy. Worldwide, "omics" studies such as genomics, transcriptomics, metabolomics and proteomics are being conducted to better understand the disease biology and risk factors of CKD. In Singapore, the Diabetes Study in Nephropathy and other Microvascular Complications was launched in 2017 with the aim of improving the understanding of DKD and to reduce its prevalence by 30% over 5 years. It is the biggest local study to examine "omics" studies in DKD. Another area of interest is gut microbiome and gut-kidney axis and their association with CKD progression and cardiovascular risk. More results are expected in this area in the near future.

In the local renal and primary healthcare community, there is a move towards a collaborative population-based database to collect real-world data to improve the health and outcomes of CKD patients in Singapore. There is a role for more artificial intelligence-assisted prediction models with dynamic variables to more accurately predict the risk of non-CKD patients developing CKD in the future, and risks of CKD reaching ESKD, cardiovascular outcomes and mortality. Other areas of focus in research include CKD health service and qualitative research to investigate CKD work processes and CKD patients' perception to improve patient care, and value-based research to investigate the value of healthcare interventions from the perspectives of the patient, healthcare system and community.

With a deeper understanding of the causes and pathogenesis of CKD, there is a need to consider more public health measures to tackle some of the modifiable contributors to the disease burden of CKD which include diabetes, hypertension and obesity. War on Diabetes is a good start to create an impact on the changing landscape of CKD in Singapore, but more interventions can be considered. Mandatory reformulation of processed food to decrease their salt and sugar content, and salt and sugar taxes are some measures that can be considered. In a systemic review of dietary salt reduction policies by Hyseni et al, they found that population-wide policies such as mandatory reformulation generally achieved larger reductions in population-wide salt consumption than interventions that were directed at the individual.[36] Many countries had initiated sugar tax for sugar-sweetened beverages and this was associated with a mean decline in beverage purchases and dietary intake of 10.0%.[37] We can consider a comprehensive multi-pronged intervention that involves mandatory reformulation and sugar and salt tax, in addition to the current education media campaign and food labelling. The financial gain from sugar and salt

taxes can be awarded to industry players who comply with mandatory reformulation, provide infrastructure and subsidies to industry players who provide healthy food (such as high efficiency urban vegetable farms) or exercise (such as gyms) and the general public who comply with the healthy lifestyle campaign. With the high penetration rate of smartphone use in the local population, compliance to healthy lifestyle by the general public can be tracked and duly rewarded.

These are exciting times in the management of CKD with new discoveries of its pathogenesis, diagnostics and therapies. Strong and sustained collaborative efforts by all stakeholders are critical to maintain the initiatives designed to improve the health and outcomes of CKD population in Singapore. Recent national primary preventive programmes like War on Diabetes will also likely have a major impact on the changing landscape of CKD in Singapore. However, it will take decades before we know whether any of these advances prove meaningful. As Johann Wolfgang von Goethe once said, "What is not started today is never finished tomorrow". On this World Kidney Day 2020, we can make an impact on CKD by acting together as a nation.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3: 1–150.
2. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 164:659–63.
3. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease–a systematic review and meta-mnalysis. PLoS One 2016;11:e0158765
4. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151–210.
5. Sabanayagam C, Lim SC, Wong TY, Lee J, Shankar A, Tai ES. Ethnic disparities in prevalence and impact of risk factors of chronic kidney disease. Nephrology Dialysis Transplantation 2010;25:2564–70.
6. Low SK, Sum CF, Yeoh LY, Tavintharan S, Ng XW, Lee SB et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Ann Acad Med Singapore 2015;44:164–71.
7. Wong LY, Liew AST, Weng WT, Lim CK, Vathsala A, Toh MPHS. Projecting the burden of chronic kidney disease in a developed country and its implications on public health. Int J Nephrol 2018;2018:5196285.
8. Ministry of Health, Singapore. Principal causes of death 2016–2018. Available at: https://www.moh.gov.sg/resources-statistics/singapore-health-facts/principal-causes-of-death. Accessed on 24 February 2020.
9. National Registry of Diseases Office, Singapore. Singapore Renal Registry Annual Report 2017. Available at: https://www.nrdo.gov.sg/publications/kidney-failure. Accessed on 24 February 2020.
10. Ministry of Health, Singapore. War on Diabetes Summary Report 2016–2019. Available at: https://www-moh-gov-sg-admin.cwp.sg/docs/librariesprovider5/war-on-diabetes/wod_public_report.pdf. Accessed on 24 February 2020.
11. Ruospo M, Saglimbene VM, Palmer SC, De Cosmo S, Pacilli A, Lamacchia O, et al. Glucose targets for preventing diabetic kidney disease and its progression. Cochrane Database Syst Rev 2017;6:CD010137.
12. Hardy ST, Zeng D, Kshirsagar AV, Viera AJ, Avery CL, Heiss G. Primary prevention of chronic kidney disease through population-based strategies for blood pressure control: the ARIC study. J Clin Hypertens 2018;20:1018–26.
13. Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004; 351:1941–51.
14. Haller H, Ito S, Izzo Jr JL, Januszewicz A, Katayama S, Menne J, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–17.
15. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–34.
16. Taghavi M, Sadeghi A, Maleki V, Nasiri M, Khodadost M, Pirouzi A, et al. Adherence to the dietary approaches to stop hypertension-style diet is inversely associated with chronic kidney disease: a systematic review and meta-analysis of prospective cohort studies. Nutr Res 2019;72:46–56.
17. Komenda P, Ferguson TW, Macdonald K, Rigatto C, Koolage C, Sood MM, et al. Cost-effectiveness of primary pcreening for CKD: a systematic review. Am J Kidney Dis 2014;63:789–97.
18. National Healthcare Group Polyclinics, Singapore. NEMO slows kidney function decline in diabetic patients. Transform Care 2013, Issue 3. Available at: https://www.nhgp.com.sg/uploadedFiles/NewsLetter/2010/Transform%20Care%20Issue%203.pdf. Accessed on 24 February 2020.
19. Teo BW, Toh QC, Xu H, Yang AY, Lin T, Li J, et al. Dietary protein intake in a multi-ethnic Asian population of healthy participants and chronic kidney disease patients. Ann Acad Med Singapore 2015;44:145–9.
20. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019 Med 2019;380:2295–306.
21. Neuen BL, Jardine MJ, Perkovic V. Sodium-glucose cotransporter 2 inhibition: which patient with chronic kidney disease should be treated in the future? Nephrol Dial Transplant 2020;35:i48–55.
22. Heerspink H, Stefansson BV, Chertow GM, Correa-Rotter R, Greene T, Hou FF, et al. Rationale and protocol of the Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomized controlled trial. Nephrol Dial Transplant 2020;35:274–82.
23. Herrington WG, Preiss D, Haynes R, von Eynatten M, Staplin N, Hauske SJ, et al. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. Clin Kidney J 2018;11:749–61.
24. Floege J, Barbour SJ, Cattran DC, Hogan JJ, Nachman PH, Tang S, et al. Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:268–80.
25. Rovin BH, Caster DJ, Cattran DC, Gibson KL, Hogan JJ, Moeller MJ, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2019;95:281–95.
26. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration

rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073–81.

27. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int 2011;80:93–104.
28. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA 2011;305:1553–9.
29. Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. JAMA 2016 2016;315:164–74.
30. Wang Y, Nguyen FNHL, Allen JC, Lew JQL, Tan NC, Jafar TH. Validation of the kidney failure risk equation for end-stage kidney disease in Southeast Asia. BMC Nephrol 2019;20:451.
31. Grams ME, Sang Y, Ballew SH, Carrero JJ, Djurdjev O, Heerspink H, et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int 2018;93;1442–51.
32. Wright Jr JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco, MV, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–16.
33. Garrison SR, Kolber MR, Korownyk CS, McCracken RK, Heran BS, Allan GM. Blood pressure targets for hypertension in older adults. Cochrane Database Syst Wright Jr JT, Rev 2017;8:CD011575.
34. Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–85.
35. Lv J, Ehteshami P, Sarnak MJ, Tighiouart H, Jun M, Ninomiya T, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ 2013;185:949–57.
36. Hyseni L, Elliot-Green A, Lloyd-Williams F, Kypridemos C, O' Flaherty M, McGill R, et al. Systematic review of dietary salt reduction policies: evidence for an effectiveness hierarchy? PLoS One 2017;12:e0177535.
37. Teng AM, Jones AC, Mizdrak A, Signal L, Genç M, Wilson N. Impact of sugar-sweetened beverage taxes on purchases and dietary intake: systematic review and meta-analysis. Obes Rev 2019;20:1187–204.