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## Research: Epidemiology

# Quality of care in patients with diabetic kidney disease in Asia: The Joint Asia Diabetes Evaluation (JADE) Registry

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## Abstract

**Aims** Diabetic kidney disease independently predicts cardiovascular disease and premature death. We examined the burden of chronic kidney disease (CKD, defined as an estimated GFR < 60 ml/min/1.73 $m^2$) and quality of care in a cross-sectional survey of adults (age ≥ 18 years) with Type 2 diabetes across Asia.

**Methods** The Joint Asia Diabetes Evaluation programme is a disease-management programme implemented using an electronic portal that systematically captures clinical characteristics of all patients enrolled. Between July 2007 and December 2012, data on 28 110 consecutively enrolled patients (China: 3415, Hong Kong: 15 196, India: 3714, Korea: 1651, Philippines: 3364, Vietnam: 692, Taiwan: 78) were analysed.

**Results** In this survey, 15.9% of patients had CKD, 25.0% had microalbuminuria and 12.5% had macroalbuminuria. Patients with CKD were less likely to achieve $HbA_{1c}$ < 53 mmol/mol (7.0%) (36.0% vs. 42.3%) and blood pressure < 130/80 mmHg (20.8% vs. 35.3%), and were more likely to have retinopathy (26.2% vs. 8.7%), sensory neuropathy (29.0% vs. 7.7%), cardiovascular disease (26.6% vs. 8.7%) and self-reported hypoglycaemia (18.9% vs. 8.2%). Despite high frequencies of albuminuria (74.8%) and dyslipidaemia (93.0%) among CKD patients, only 49.0% were using renin–angiotensin system inhibitors and 53.6% were on statins. On logistic regression, old age, male gender, tobacco use, long disease duration, high $HbA_{1c}$, blood pressure and BMI, and low LDL cholesterol were independently associated with CKD (all $P < 0.05$).

**Conclusions** The poor control of risk factors, suboptimal use of organ-protective drugs and high frequencies of hypoglycaemia highlight major treatment gaps in patients with diabetic kidney disease in Asia.

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## Introduction

Diabetes mellitus is now a global pandemic as a result of population growth, ageing and increasing rates of obesity, with over 60% of affected individuals coming from Asia, mainly China and India [1]. The development of diabetes complications substantially increases healthcare expenditure, which is fivefold higher in those with advanced chronic kidney disease (CKD) compared with those without complications [2]. In many parts of the world, diabetes is now the leading cause of end-stage renal disease (ESRD) and renal replacement therapy. Reduced GFR and albuminuria have been shown to independently predict cardiovascular disease, congestive heart failure and all-cause mortality [3,4]. With the onset of CKD, there is a downstream deterioration in the metabolic milieu including anaemia, calcium–phosphate

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**What's new?**

- In this large multi-national Asia diabetes database, 15% of patients had diabetic kidney disease, over a quarter of whom had other concomitant micro- or macrovascular complications.
- Despite their inherent high vascular risk, only one third of patients with diabetic kidney disease achieved pre-specified glycaemic and/or blood pressure targets and their use of organ-protective drugs such as renin–angiotensin system inhibitors and statins was suboptimal.
- This article highlights a major treatment gap in Asian patients with diabetic kidney disease calling for greater quality improvement effort.

homeostasis disturbances and heightened inflammation, which collectively increase the risk of atherosclerosis [5].

Treatment to multiple targets has been shown to significantly lower diabetes-related complications including CKD and mortality [6,7]. International guidelines have provided evidence-based recommendations on metabolic targets and criteria for the use of life-saving drugs such as renin–angiotensin system inhibitors and statins for the prevention and treatment of diabetes complications [8]. Despite major advances in the understanding of disease progression and treatment effect as well as an expanding armamentarium of therapeutics in diabetes and cardiovascular medicine, many patients with diabetes are not managed optimally, in part due to clinical inertia and suboptimal adherence to self-care and medication [9–12].

The Joint Asia Diabetes Evaluation (JADE) programme is a web-based disease-management programme that incorporates templates for metabolic and diabetes complication screening, validated risk equations to estimate 5-year probability of major clinical events and built-in protocols to provide decision support to physicians and patients [13,14]. Since 2007, nine countries/areas across Asia have enrolled patients into the JADE programme as a quality improvement initiative and for the establishment of the Asia Diabetes Database. The primary objective of this article was to examine the clinical profile and quality of care of patients with Type 2 diabetes and CKD in Asia.

## Patients and methods

### Patients

The JADE programme is an electronic disease-management programme with templates to guide the comprehensive assessment of patients' metabolic profiles and complication status. Using built-in protocols, personalized reports are generated to inform patients and physicians on the risk profile of the patient, identify treatment gaps and provide decision support. There were no entry criteria for enrolment and patients were enrolled from diverse clinic settings including hospital-based and community clinics, and from the private and public sector. Between 1 July 2007 and 31 December 2012, the analysis included 28 110 consecutively enrolled patients aged 18 years or above with Type 2 diabetes from seven regions/areas in Asia, namely China, Hong Kong, India, Korea, Philippines, Taiwan and Vietnam, with available serum creatinine measurements. Use of the JADE portal for research and publication was approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee and the relevant institutional boards of participating sites. All patients provided informed consent for the research team to retrieve and analyse their anonymized data.

### Complication assessment

All patients were recommended to undergo detailed clinical assessments including documentation of their sociodemographic profile, metabolic risk factors, history of cardiovascular diseases and cancer, lifestyle and medication. Blood pressure and anthropometric measurements were collected. The presence of retinopathy was examined using fundoscopy or retinal photography depending on availability at the participating health centre. Peripheral sensory neuropathy was determined using a graduated tuning fork and monofilament. Sensory neuropathy was defined by two of three criteria of self-reported abnormal sensation in the lower extremities, reduced sensation to monofilament, or reduced vibration sense to tuning fork stimulation. Cardiovascular disease was defined as a history of coronary heart disease, stroke or peripheral vascular disease, the latter defined as non-traumatic lower extremity amputation, a revascularization procedure for peripheral vascular disease or an ankle–brachial index $\leq 0.9$. The ankle–brachial index threshold of 0.9 is conventionally used to define peripheral vascular disease and increased cardiovascular risks [15]. Lifestyle aspects included current and previous use of tobacco/alcohol, self-monitoring of blood glucose, regular physical exercise and adherence to a healthy diet within the previous 3 months. Adherence to regular physical exercise was indicated by self-report of physical activity at least three times per week, and adherence to a healthy diet was by simple response to yes/no question on this parameter. Hypoglycaemia was assessed by self-report of typical hypoglycaemia symptoms in the previous 3 months. Severe hypoglycaemia was defined as hypoglycaemia that required medical or non-medical third person assistance.

Blood and spot urine samples were collected for plasma glucose, $HbA_{1c}$, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, renal function test and urine albumin-to-creatinine ratio, after at least 8 h of fasting.

Hypertension was defined as systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg or concurrent use of anti-hypertensive drugs. Dyslipidaemia was defined as either LDL cholesterol ≥ 2.6 mmol/l, HDL cholesterol < 1.0 mmol/l, triglyceride ≥ 1.7 mmol/l or concurrent use of lipid-regulating drugs. Obesity was defined by BMI ≥ 30 kg/m$^2$ based on World Health Organization international definition [16]. Estimated GFR, expressed in ml/min/1.73 m$^2$, was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation. CKD was defined as eGFR < 60 ml/min/1.73 m$^2$, while ESRD was defined as eGFR < 15 ml/min/1.73 m$^2$ or a need for renal transplant or dialysis. Microalbuminuria was defined as a urine albumin-to-creatinine ratio ≥ 2.5–25.0 mg/mmol in men and ≥ 3.5–25 mg/mmol in women, and macroalbuminuria was defined as a urine albumin-to-creatinine ratio ≥ 25 mg/mmol.

### Statistical analysis

All analysis was performed using the Statistical Package for Social Science (SPSS v. 21.0, Chicago, IL, USA). For descriptive analysis, continuous variables were expressed as mean ± sd or as median [interquartile range (IQR)], and categorical variables were expressed as percentages. The proportions of patients with CKD and albuminuria in all seven regions/areas were reported separately with 95% confidence intervals (CI). Comparison of baseline demographic, clinical and biochemical data as well as use of organ-protective medications, self-management and hypoglycaemia was made between patients with and without CKD. The chi-square test was used for between-group comparison of categorical variables, *t*-test was used for normally distributed continuous variables and Kruskal–Wallis test was used for continuous variables with a skewed distribution. Multivariable logistic regression was performed to identify factors that were independently correlated with CKD. Clinical variables entered into the model were selected based on prior knowledge of possible relationships with CKD, including age, gender, tobacco use, disease duration, $HbA_{1c}$, systolic blood pressure, LDL cholesterol, BMI, waist circumference, urinary albumin-to-creatinine ratio, diabetic retinopathy and sensory neuropathy. A value of $P < 0.05$ (two-tailed) was considered significant.

## Results

In this cross-sectional cohort of 28 110 patients (China: 3415, Hong Kong: 15 196, India: 3714, Korea: 1651, Philippines: 3364, Vietnam: 692, Taiwan: 78), the mean age was 58.1 years, 54.1% were male and the mean duration of diabetes was 8.2 ± 7.6 years. The proportion of patients with CKD was 15.9% (95% CI 15.4%–16.2%), 25.0% had microalbuminuria (95% CI 24.4%–25.6%) and 12.5% had macroalbuminuria (95% CI 12.1%–13.0%). The region-specific figures are shown in Fig. 1. The frequencies of patients with CKD ranged from 2.9% (95% CI 2.4%–3.5%) in China to 39.8% (95% CI 38.3%–41.4%) in India, whereas for albuminuria, the frequencies ranged from 29.0% (95% 27.4%–30.6% CI) in China to 62.7% (95% CI 58.7%–66.6%) in Philippines.

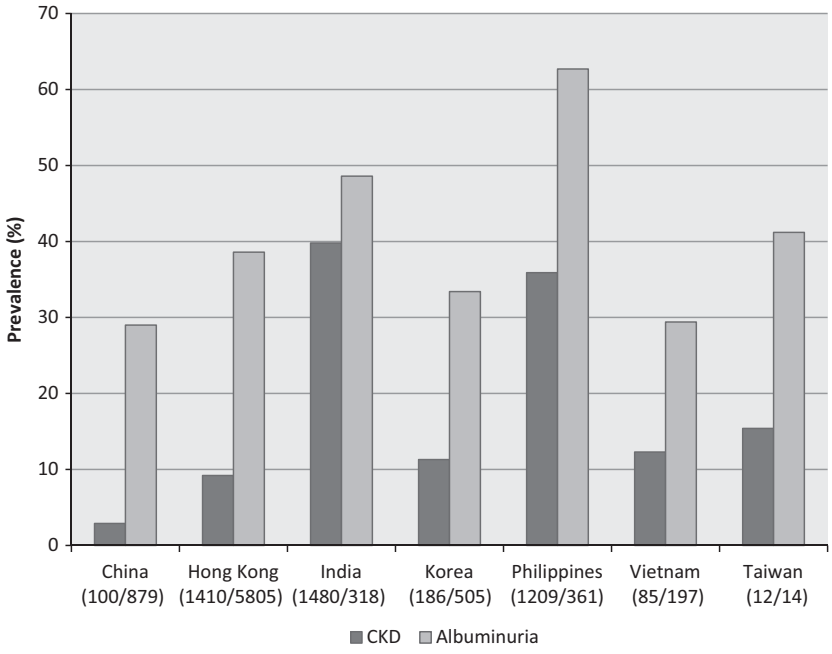


**FIGURE 1** Proportion of patients with Type 2 diabetes with chronic kidney disease and albuminuria in seven regions/areas in Asia. The denominator for the percentages is the number of patients with available estimated glomerular filtration rate or available urine albumin-to-creatinine ratio measurements. Data in parentheses are the number of patients with CKD/number of patients with albuminuria.

**Table 1** Clinical characteristics of patients with Type 2 diabetes with and without chronic kidney disease (CKD) enrolled from seven regions into the Joint Asia Diabetes Evaluation Program between 2007 and 2012

| | CKD ($n$ = 4482) | Non-CKD ($n$ = 23 628) | $P$ |
|---|---|---|---|
| *Demographics* | | | |
| Age (years) | 64.4 ± 10.6 | 57.0 ± 11.2 | < 0.001 |
| Male (%) | 49.3 | 55.1 | < 0.001 |
| Education (%) | | | |
| Primary | 33.2 | 28.1 | < 0.001 |
| Middle school | 19.7 | 31.8 | |
| Higher school | 14.8 | 13.3 | |
| College | 32.3 | 26.8 | |
| Smoking (%) | | | |
| Ex | 18.0 | 28.1 | < 0.001 |
| Current | 15.0 | 8.2 | |
| *Metabolic profile* | | | |
| Disease duration (years) | 11.6 ± 8.5 | 7.6 ± 7.2 | < 0.001 |
| BMI (kg/m$^2$) | 25.8 ± 4.2 | 25.7 ± 5.6 | 0.295 |
| Waist (cm) | | | |
| Male | 89.0 ± 11.0 | 90.8 ± 10.4 | < 0.001 |
| Female | 85.5 ± 14.0 | 86.0 ± 10.9 | 0.193 |
| Systolic blood pressure (mmHg) | 137.8 ± 20.4 | 131.1 ± 17.7 | < 0.00‘ |
| Diastolic blood pressure (mmHg) | 78.7 ± 10.7 | 78.3 ± 10.3 | 0.013 |
| $HbA_{1c}$ [mmol/mol (%)] | 62 ± 14 (7.8 ± 1.8) | 61 ± 14 (7.7 ± 1.8) | < 0.001 |
| Fasting plasma glucose (mmol/l) | 8.1 ± 3.2 | 8.1 ± 2.8 | 0.898 |
| Total cholesterol (mmol/l) | 4.6 ± 1.3 | 4.7 ± 1.1 | < 0.001 |
| LDL cholesterol (mmol/l) | 2.8 ± 1.0 | 2.7 ± 0.9 | 0.329 |
| Triglyceride (mmol/l) | 1.6 ±1.1 | 1.3 ± 1.1 | < 0.001 |
| HDL cholesterol (mmol/l) | | | |
| Male | 1.1 ± 0.3 | 1.2 ± 0.3 | < 0.001 |
| Female | 1.2 ± 0.4 | 1.4 ± 0.4 | < 0.001 |
| Estimated GFR (ml/min/1.73 m$^2$) | 46.7 (18.2) | 106.5 (36.5) | < 0.001 |
| Urine albumin-to-creatinine ratio (mg/mmol) | 26.8 (128.6) | 1.8 (5.3) | < 0.001 |
| Hypertension (%) | 95.4 | 80.7 | < 0.001 |
| Dyslipidaemia (%) | 93.0 | 87.0 | < 0.001 |
| General obesity (%) | 12.7 | 12.6 | 0.815 |
| Central obesity (%) | 55.0 | 61.3 | < 0.001 |
| *Diabetes complications* | | | |
| Microalbuminuria (%) | 27.6 | 24.7 | 0.004 |
| Macroalbuminuria (%) | 47.2 | 8.8 | < 0.001 |
| Retinopathy (%) | 26.2 | 20.1 | < 0.001 |
| Sensory neuropathy (%) | 29.0 | 7.7 | < 0.001 |
| Coronary heart disease (%) | 26.6 | 8.7 | < 0.001 |
| Stroke (%) | 7.2 | 4.5 | < 0.001 |
| Peripheral vascular disease (%) | 9.1 | 6.4 | < 0.001 |
| *Treatments* | | | |
| Lifestyle modification only (%) | 27.4 | 21.5 | < 0.001 |
| Metformin (%) | 40.3 | 64.2 | < 0.001 |
| Sulfonylurea (%) | 35.1 | 35.0 | 0.859 |
| Thiazolidinediones (%) | 6.7 | 7.3 | 0.161 |
| DPP-4 inhibitors (%) | 9.8 | 4.8 | < 0.001 |
| Glucagon-like peptide-1 agonist (%) | 4.3 | 5.4 | 0.001 |
| Insulin (%) | 30.9 | 13.3 | < 0.001 |
| Anti-hypertensive drug (%) | 58.8 | 37.6 | < 0.001 |
| Renin–angiotensin system blockers (%) | 49.0 | 28.8 | < 0.001 |
| Statins (%) | 53.6 | 37.0 | < 0.001 |
| Self-reported lifestyle modification | | | |
| Diet compliance (%) | 45.9 | 52.2 | < 0.001 |
| Physical activity ≥ 3 times per week (%) | 43.6 | 48.3 | < 0.001 |
| Self-monitoring of blood glucose (%) | 53.6 | 59.4 | < 0.001 |
| Hypoglycaemic events ≥ once per month (%) | 18.9 | 8.2 | < 0.001 |
| Severe hypoglycaemia in the previous 3 months | 2.3 | 0.9 | < 0.001 |
| *Attainment of treatment targets* | | | |
| $HbA_{1c}$ < 53 mmol/mol (7.0%) (%) | 36.0 | 42.3 | < 0.001 |
| Blood pressure < 130/80 mmHg (%) | 20.8 | 35.3 | < 0.001 |
| LDL cholesterol < 2.6 mmol/l (%) | 49.2 | 46.2 | < 0.001 |
| One target attained | 76.5 | 79.4 | < 0.001 |

**Table 1** (*Continued*)

| | CKD ($n$ = 4482) | Non-CKD ($n$ = 23 628) | $P$ |
|---|---|---|---|
| Two targets attained | 28.2 | 37.3 | < 0.001 |
| Three targets attained | 3.6 | 8.3 | < 0.001 |

Central obesity: waist circumference ≥ 90 cm in men or ≥ 80 cm in women. General obesity: BMI ≥ 30 kg/m$^2$. Dyslipidaemia: LDL cholesterol ≥ 2.6 mmol/l, triglyceride ≥ 1.7 mmol/l, HDL < 1.0 mmol/l or use of lipid-lowering drugs. Hypertension: known history of hypertension, systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 80 mmHg or use of anti-hypertensive drugs. Chronic kidney disease: eGFR < 60 ml/min/1.73 m$^2$. Microalbuminuria: urine albumin-to-creatinine ratio 2.5–25 mg/mmol in men or 3.5–25 mg/mmol in women. Macroalbuminuria: urine albumin-to-creatinine ratio > 25 mg/mmol. Retinopathy: presence of background or advanced retinopathy and/or maculopathy. Sensory neuropathy: two of three of reduced monofilament sensation, reduced vibration sensation to graduated tuning fork testing or abnormal sensation in lower limbs. Coronary heart disease: history of myocardial infarction or coronary intervention. Peripheral vascular disease: non-traumatic leg amputation, peripheral revascularization or ankle–brachial index < 0.9. Severe hypoglycaemia: self-report of hypoglycaemic episode requiring medical or non-medical third person assistance. One target: achieving either one of three targets of $HbA_{1c}$ < 53 mmol/mol (7.0%), blood pressure < 130/80 mmHg or LDL cholesterol < 2.6 mmol/l. Two targets: achieving two of three targets of $HbA_{1c}$ < 53 mmol/mol (7.0%), blood pressure < 130/80 mmHg or LDL cholesterol < 2.6 mmol/l. Three targets: achieving all three targets of $HbA_{1c}$ < 53 mmol/mol (7.0%), blood pressure < 130/80 mmHg or LDL cholesterol < 2.6 mmol/l.

The mean eGFR was 46.7 ml/min/1.73 m$^2$ in patients with CKD and 106.5 ml/min/1.73 m$^2$ in those without. Among the group with CKD, 81.7% (95% CI 80.6%–82.8%) had an eGFR between 30 and 60 ml/min/1.73 m$^2$, 14.9% (95% CI 13.9%– 16.0%) had an eGFR between 15 and 30 ml/min/1.73 m$^2$, and 3.3% (95% CI 2.8%–3.9%) had an eGFR of < 15 ml/min/1.73 m$^2$. Patients with CKD were older, had a longer disease duration, higher $HbA_{1c}$, systolic blood pressure and triglyceride levels, but similar LDL cholesterol levels and BMI. They were also more likely to have macroalbuminuria, microalbuminuria, retinopathy, sensory neuropathy and a history of coronary heart disease and stroke compared with those without CKD (Table 1).

Patients with CKD were less likely to be treated with metformin, but were more likely to be given dipeptidyl peptidase-4 (DPP-4) inhibitor and insulin. Although more patients with CKD were prescribed anti-hypertensive drugs, renin–angiotensin system inhibitors and statins, the proportion of patients using these agents fell short of the proportion of patients with hypertension, albuminuria and dyslipidaemia. Only 62.0% (95% CI 60.9%–63.5%) of patients identified as having hypertension were on anti-hypertensive drugs and only 64.3% (95% CI 62.8%–65.8%) of those with dyslipidaemia were taking statins (Fig. 2f–g). Similarly, although 74.8% (95% CI 73.0%–76.7%) of patients with CKD had albuminuria, renin–angiotensin system inhibitors were prescribed in just 50.8% (95% CI 48.3%–53.3%) of these patients (Fig. 2e) and in 49.0% of all patients with CKD. Under-treatment despite clinical indication was observed in all regions (Fig. 2e–g).

The proportions of patients attaining targets of $HbA_{1c}$ < 53 mmol/mol (7.0%) and blood pressure < 130/80 mmHg were lower, whereas the proportion of patients of reaching LDL cholesterol < 2.6 mmol/l was higher in the CKD group compared with the non-CKD group. Separated by regions, a similar trend was observed in most, although not all, reaching statistical significance (Fig. 2a–d). In the CKD group, 36% of patients reached the $HbA_{1c}$ target, 20.8% reached the blood pressure target, 49.6% reached the LDL cholesterol target and 3.6% reached all three targets. The respective figures for the non-CKD group were 42.3%, 35.3%, 46.2% and 8.3%. Apart from having worse glycaemic control, 18.9% of patients with CKD self-reported hypoglycaemic events at least once a month over the previous 3 months and 2.3% had severe hypoglycaemia. The respective figures in those without CKD were 8.2% and 0.9%. Compared with patients without CKD, those with CKD were more likely to be active smokers and less likely to adhere to a balanced diet, perform regular exercise or self-monitor blood glucose.

Using multiple logistic regression, old age, long disease duration, previous tobacco use, high $HbA_{1c}$, systolic blood pressure, BMI and urinary albumin-to-creatinine ratio, but low LDL cholesterol, diabetic retinopathy and sensory neuropathy, were significantly associated with CKD (Table 2). Variables entered but not selected by the model included gender, current tobacco use and waist circumference.

## Discussion

In this large and comprehensive dataset of patients with Type 2 diabetes across Asia, one in six patients had CKD and up to 40% had albuminuria. Patients with CKD had worse metabolic control and were more likely to have other vascular complications including coronary heart disease and stroke. Despite being at high risk for cardiovascular disease and mortality, fewer patients with CKD attained glycaemic and blood pressure targets. There was also under-usage of life-saving drugs and suboptimal self-care, with one in five reporting recent episodes of hypoglycaemia.

### Inter-ethnic differences in prevalence of diabetic kidney disease

Several epidemiological studies have examined the prevalence of diabetic kidney disease in populations of mixed ethnicities [17–19]. An international multi-ethnic study

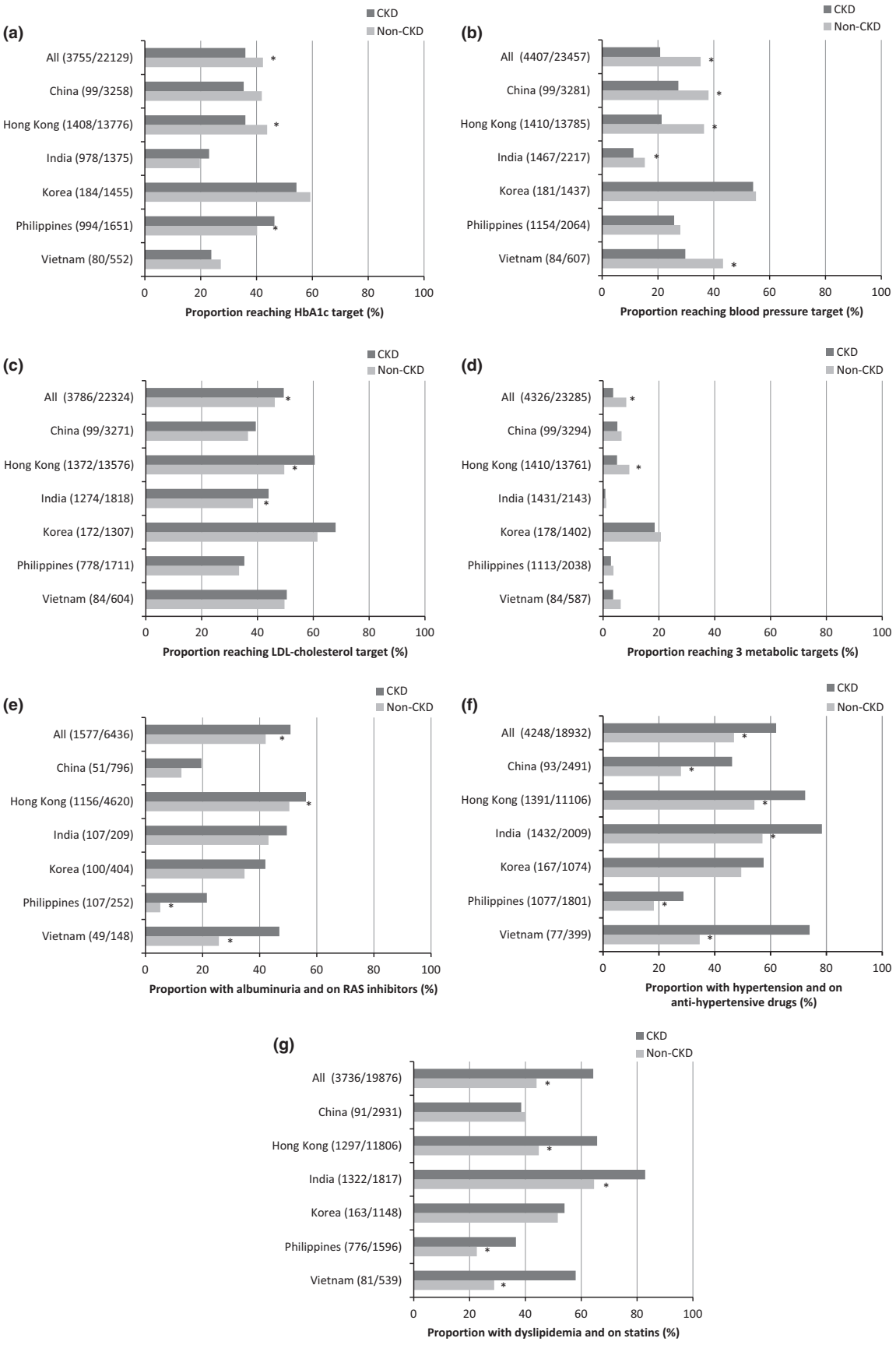

**FIGURE 2** (a–d) Proportion of patients with Type 2 diabetes with and without chronic kidney disease reaching: $HbA_{1c}$ target < 53 mmol/mol (7.0%) by region (a), blood pressure target < 130/80 mmHg by region (b), low density-lipoprotein (LDL)-cholesterol target < 2.6 mmol/l by region (c), and (d) all three metabolic targets of $HbA_{1c}$ < 53 mmol/mol (7.0%), blood pressure < 130/80 mmHg and low density-lipoprotein cholesterol < 2.6 mmol/l by region. (e) Proportion of patients with Type 2 diabetes and albuminuria with and without chronic kidney disease being treated with renin-angiotensin system inhibitors. (f) Proportion of patients with Type 2 diabetes and hypertension with and without chronic kidney disease being treated with anti-hypertensive drugs. (g) Proportion of patients with Type 2 diabetes and dyslipidaemia with and without chronic kidney disease treated with statins. The number of patients with/without CKD with valid data included in analysis is indicated in parentheses after the country/region name. Because of the low number of patients with valid data in Taiwan, the data from this region are not shown. *$P < 0.05$ for comparison between patients with and without CKD.

enrolling over 32 000 patients from 33 countries reported that Asians and Hispanics were more likely to have micro- and macroalbuminuria compared with their non-Hispanic European counterparts. In this earlier report, albuminuria was present in 55% of Asians and 40% of Europeans, despite younger age and shorter disease duration in the former group [19]. In another survey sampling 5500 patients with Type 2 diabetes and concomitant hypertension in 10 Asian countries, albuminuria was recorded in 58% of patients with a mean disease duration of 7 years [17]. In both of these former studies, the numbers of patients with low GFR were not reported. In the current cohort, we documented albuminuria in 37% of patients and CKD in 16% of patients, although there were marked disparities across regions with the lowest rates of CKD and albuminuria in China and the highest rates in India and Philippines. The excess of diabetic kidney disease in Filipinos relative to other Asian ethnic groups in the present analysis concurs with observations from other contemporary studies, whereas higher frequencies in Asian Indians have been reported less consistently [18,20]. Examination of a large managed care diabetes database in the USA showed that among the Asian subgroups, Filipinos had higher prevalence of CKD (37.9%) than both Chinese (27.6%) and Asian Indians (24.8%), and Asians overall had greater odds of having proteinuric CKD than Europeans [20]. In a mixed ethnic cross-sectional population cohort in Singapore, Asian Indians had a comparatively higher frequency of CKD (17.6%) than Chinese (11.4%) [21]. Although the inter-ethnic disparities observed may reflect inherent biological differences with respect to predisposition to progressive diabetic renal injury and response to therapy, factors including treatment, risk factors control and lifestyle are also relevant in determining the risks of developing complications. It should be pointed out that both Philippines and India are largely private in health service provision, whereas most other regions have a predominant public or subsidized healthcare system. It is therefore possible that in these regions, individuals with advanced disease had greater incentives to participate in the programme and this may have contributed to the disproportionately higher rates of complications in these populations.

**Table 2** Multivariable logistic regression to show the association of clinical factors with chronic kidney disease in patients with Type 2 diabetes

| Clinical variables | Odds ratio (95% CI) | *P* |
|---|---|---|
| Age | 1.08 (1.08–1.09) | < 0.001 |
| Male | 0.92 (0.80–1.06) | 0.236 |
| Ex smoking | 1.21 (1.04–1.40) | 0.015 |
| Current smoking | 0.84 (0.67–1.05) | 0.132 |
| Disease duration | 1.04 (1.04–1.05) | < 0.001 |
| $HbA_{1c}$ | 1.06 (1.02–1.10) | 0.003 |
| Systolic blood pressure | 1.01 (1.00–1.01) | 0.002 |
| LDL cholesterol | 0.91 (0.85–0.98) | 0.007 |
| BMI | 1.04 (1.01–1.06) | 0.004 |
| Waist circumference | 1.01 (1.00–1.02) | 0.127 |
| Urine albumin-to-creatinine ratio | 1.01 (1.01–1.01) | < 0.001 |
| Diabetic retinopathy | 1.29 (1.15–1.46) | < 0.001 |
| Sensory neuropathy | 1.67 (1.41–1.98) | < 0.001 |

Retinopathy: presence of background or advanced retinopathy and/or maculopathy. Sensory neuropathy: two of three of reduced monofilament sensation, reduced vibration sensation to graduated tuning fork testing, or abnormal sensation in lower limbs.

### Metabolic control in patients with diabetic kidney disease

Several large-scale studies have now confirmed that concurrent CKD increased the risk of major cardiovascular event and related death by two to threefold in patients with diabetes [22]. The STENO study showed that intensive global risk factor control through medication and behaviour modification effectively prevented cardiovascular disease and premature death in high-risk individuals with albuminuria [6]. Despite the preventable nature of these complications, in the USA, only 18% of patients with Type 2 diabetes reached triple targets of glycaemia, blood pressure and cholesterol [10]. Complex care protocols, clinical inertia, patient non-compliance and lack of care coordination are major impediments to successful management of chronic disease [23]. In this regard, we further noted that patients with CKD were less likely to perform self-monitoring and had worse adherence to diet and regular physical exercise than the non-CKD group. Parallel to the under-performance in self-care activities, risk factor control was worse in patients with CKD than those without. Significantly fewer patients with CKD achieved all three metabolic goals (3.6% vs. 8.3%), driven by lower frequencies of target attainment in $HbA_{1c}$ and blood pressure.

### Hypoglycaemia and diabetic kidney disease

Optimization of glycaemic control is challenging and problematic in patients with CKD for a number of reasons. With a decline in renal function, the available options of anti-diabetic agents become limited because many agents are excreted via the renal route raising the potential for drug accumulation. Irrespective of the anti-diabetic regimen used, patients with CKD are at greater risk of hypoglycaemia, which, *per se*, is a major barrier to meeting glycaemic targets [24]. In our cohort, 18% of patients with CKD reported a hypoglycaemic event at least once a month, a frequency twice that seen in those without CKD. The association of hypoglycaemia with mortality has been well reported in both cohort studies and randomized clinical trials [25,26], although it remains unclear as to whether hypoglycaemia is directly causal or is a surrogate for advanced disease.

### Blood pressure control in patients with CKD

In this survey, 95% of patients with CKD had hypertension similar to that reported previously [27]. However, only 20% of patients with CKD in our cohort achieved a blood pressure target of < 130/80 mmHg, whereas the same target was reached in over 40% of people in a recent analysis of the NHANES database of 4926 adults with self-reported diabetes between 1988 and 2010 [10]. Meticulous control of blood pressure has been shown to retard the progression of CKD and reduce the incidence of cardiovascular events, particularly stroke [28,29]. Renin–angiotensin system blockers have additional renal protective properties beyond blood pressure lowering. Among high-risk patients with persistent albuminuria and impaired renal function, renin–angiotensin system blockers were effective in lowering urinary albumin excretion and delaying time to ESRD [30,31]. It is further noteworthy that Asians are as responsive to renin–angiotensin system blockers as Caucasians [32]. In the current database, we found that anti-hypertensive drugs were prescribed in only 60% and renin–angiotensin system blockers in half of patients with existing hypertension, drawing attention to gross under-use of these agents despite unequivocal renal benefits.

### Limitations

The strength of our study is the large sample size involving multiple Asian countries and comprehensive data collection under a protocol. To our knowledge, few studies have specifically addressed metabolic control in diabetic patients with CKD. Our study has the following limitations. First, patients enrolled in the JADE programme may not be representative of the diabetic population in their respective countries. Although the main consideration of the JADE programme was quality improvement in real-world practices, given limitations in programme resources and the large number of regions involved, it was not possible to ensure unbiased sampling. The selection and participation of physicians and patients in the programme was subjected to influences such as physicians' motivation and patients' readiness to be enrolled. Heterogeneity also existed in the proportion of private vs. public clinics, and specialty vs. non-specialty practices. Despite the diversity, the persistent treatment gaps in patients with CKD in all areas highlighted the challenges in managing this complex condition. Second, we used fixed targets as one of the care outcome measures in this analysis. We acknowledge that individualized glycaemic target is now advocated over a 'one-size-fit-all' target taking into consideration age, disease duration, comorbidities and life expectancy [7]. Indeed, there is a scarcity of data on the optimal glycaemic target in patients with CKD. Previous studies that examined intensive vs. conventional glycaemic control have not specifically included patients with established CKD. The shift from a target-driven treatment algorithm to a risk-based strategy also pertains to the management of LDL cholesterol [33]. Although we recognize the over-simplification of quantifying care quality by targets alone, we contend that in epidemiological research, the use of set targets enables broad examination of performance and comparison between regions and across time. Third, there is a limitation on the standardization of laboratory assays due to the participation of multiple countries. Given the large number of sites, each with their own affiliated laboratory, we were also not able to obtain specific details on assay performance and accreditation of the individual laboratory. Up to 25% of patients were not tested for albuminuria, possibly due to reasons such as limitations in laboratory support, a lack of financial coverage or an unwillingness to pay. Fourth, because this was a cross-sectional analysis, we were unable to examine the prognosis of patients with diabetic kidney disease, particularly in relation to how metabolic control may influence progression of the disease to major vascular and renal outcomes in this group of patients.

## Conclusions

In this multinational survey, we have documented the high proportions of Asian patients with diabetic kidney disease who had poor risk factor control, under-usage of life-saving drugs, suboptimal self-management and frequent hypoglycaemia. These data aim to raise awareness regarding the importance of periodic assessment for these silent risk factors and complications to reduce clinical inertia and improve self-management. The incomplete data collection in some of these patients also highlights the pressing need to address system factors in our attempt to reduce the burden of these comorbidities.

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### Competing interests

Juliana C. Chan and Chun Chung Chow are Chief Executive Counsellors of the ADF, Andrea O. Luk is the Deputy Medical Director of the ADF, and Juliana C. Chan is the Chief Executive Officer of ADF, all on a pro bono basis.

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