Diabetic kidney disease is defined as albuminuria, reduced estimate glomerular filtration rate (eGFR) or both in the setting of diabetes. It develops in approximately 30-40% of patients with type 2 diabetes, and the prevalence of chronic kidney disease (CKD) in patients with type 2 diabetes has been reported to be around 18.0% in those with advanced CKD stages (16.8% in CKD stage 3; 1.2% in CKD 4 and 5). Given that the risk of major adverse cardiovascular events (MACEs) is higher in both diabetic and non-diabetic patients with CKD stage 3-5 and that a decrease in eGFR has also been associated with a higher risk of MACEs in patients with type 2 diabetes, delaying or preventing the progression of CKD in diabetic patients is of the utmost importance. Several risk factors for

**Introduction**

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**ABSTRACT**

**Background and Aims:** Subjects with diabetes are prone to a rapid decline in renal function and major adverse cardiovascular events when they reach chronic kidney disease (CKD) stage 3. This study aimed to identify modifiable risk factors associated with the progression of CKD in this population. **Settings and Design:** An observational cohort study. **Methods and Materials:** A total of 320 type 2 diabetic patients with CKD stage 3 registered in the shared-care-system in our hospital in 2010 were regularly followed up for 7 years. Demographic, laboratory, medication, and fundus examination data of these subjects were collected and analyzed. **Statistical Analysis Used:** Cox regression was used to identify factors associated with changes in CKD stage. **Results:** During the 7-year follow-up period, 204 cases (63.7%) remained at CKD stage 3 while 79 cases (24.7%) progressed to stage 4 or 5 and 37 cases (11.6%) improved to stage 1 or 2. The change in estimated glomerular filtration rate (eGFR) in the first 2 years and variations in glycated hemoglobin (HbA1c) over 7 years were independent factors of both progression (hazard ratio (HR) 1.098 and 1.710, respectively) and improvement (HR 0.919 and 0.231, respectively) of CKD stage. Variations in systolic blood pressure (SBP) was also found as an independent factor for progression of renal function (HR 1.052). **Conclusions:** Our results demonstrated that fluctuations in HbA1c and SBP, and changes in eGFR during the first 2 years of treatment were associated with the long-term renal outcomes in type 2 diabetic patients with CKD stage 3.

**KEY WORDS:** Chronic kidney disease, type 2 diabetes mellitus, variation in blood pressure, variation in HbA1c

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the progression of diabetic kidney disease have been identified, of which hyperglycemia and hypertension are the two most prominent, in addition to other factors such as proteinuria, diabetic retinopathy, obesity and dietary factors.[2,7-9] However, the results of previous studies with regards to the risk factors for progression have been inconsistent.[10] Therefore, the aim of this study was to identify modifiable risk factors associated with the progression of renal impairment, which may lead to new strategies to manage diabetic patients with CKD.

**Methods**

The shared-care-program is a team-care package for patients with diabetes in Taiwan.[11] Thorough education is provided by the endocrinologists, diabetes educators and dietitians, and the regular laboratory and fundus examinations are provided and recorded in the registration system. We reviewed information from the shared-care-system at a university hospital in Northern Taiwan, and enrolled patients with both type 2 diabetes mellitus and stage 3 CKD who were registered in the system from 1 January 2010 to 31 December 2010. All of the enrolled patients remained registered in the shared-care-program for a minimum of 7 years until 31 December 2017. Their demographic, laboratory, medication and fundus report data during the 7-year study period were collected and analyzed. Ethical approval was given by the Chang Gung Medical Foundation Institutional Review Board (201900489B0). We excluded patients aged younger than 18 years, those with type 1 diabetes mellitus, those who had acute kidney injury, and those with very severe hypertension within 6 months duration before enrollment.

Variability in visit-to-visit systolic blood pressure (SBP) was calculated as standard deviation based on SBP from consecutive visits at our clinics during the 7-year study period. Variabilities in body mass index (BMI), total cholesterol (TC), low-density lipid cholesterol (LDL-C), and glycated hemoglobin (HbA1c) were calculated as standard deviation based on these parameters obtained during the 7-year study period. Serum creatinine was measured using traceable isoelution mass spectrometry (IDMS). Albuminuria and proteinuria were defined as urine albumin creatinine ratio (UACR) >= 30 mg/g and urine total protein creatinine ratio (UPCR) >= 200 mg/g, respectively. Microalbuminuria and microproteinuria were defined as UACR 30 ~ 300 mg/g and UPCR 200 ~ 885 mg/g, respectively, and macroalbuminuria and macroproteinuria were defined as UACR > 300 mg/g and UPCR > 885 mg/g, respectively. Albuminuria/proteinuria measurements were repeated within 3 months, and the CKD stage was confirmed in all 320 patients. Three categories of urine albumin/protein findings were used in this study: normal, microalbuminuria/microproteinuria, and macroalbuminuria/macroproteinuria.

Blood pressure was measured in all of the patients at every visit at a brachial level after 15 minutes of rest in a sitting position using a digital blood pressure monitor device (CARESCAPE V100, GE Company, Tampa, Florida, US) and a cuff of appropriate size. If the SBP was > 180 mmHg, another measurement was performed after a further 15 minutes of rest.

A digital retinal camera with retinal imaging control software, Canon CR-2 with software NM2 (version 4.1) manufactured by Canon Inc. (Ota city, Tokyo, Japan), was used to screen for diabetic retinopathy and acquire images without pupil dilation. Four categories of fundus findings were used in this study: normal, proliferative diabetic retinopathy (PDR), non-proliferative diabetic retinopathy (NPDR), and undiagnosed (including cataracts and poor image).

The effect of each drug on renal outcomes was presented as the duration and percentage of exposure to that drug. The use of non-steroidal anti-inflammatory drugs (NSAIDs) was defined as exposure for any duration and presented as days of exposure, while the use of other medications including dipeptidyl peptidase 4 inhibitors (DPP4is), sodium glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP-1Ras), renin-angiotensin-aldosterone system inhibitors (RAASis) and diuretics was defined as exposure to the specific classification of medication for any duration during the 7-years study period and presented as months of exposure. The doses of DPP4i, RAASi, SGLT2is, GLP-1Ras and diuretics were prescribed as the optimal dose for patients with different stages of CKD during the 7-year study period.

The study outcome was the stage of CKD at the end of the 7-year study period (in 2017). The patients were then classified into four groups according to the stage of CKD at the end of the 7-year study period as those with CKD stage 1 + 2 (improvement), those with CKD stage 3a, those with CKD stage 3b, and those with CKD stage 4 + 5 (progression). We analyzed the factors which may have been associated with an improvement or progression of CKD stage.

The CKD stage was defined according to the Modification of Diet in Renal Disease (MDRD) Study Group criteria as follows: CKD stage 1 eGFR ≥90; stage 2 eGFR ≥60 but <90; stage 3a eGFR ≥45 but <60; stage 3b eGFR ≥30 but <45; stage 4 eGFR ≥15 but <30; and stage 5 eGFR <15 (mL/min/1.73 m²). In this study, ∆eGFR/2y was defined as the change in eGFR in the first 2 years of observation (the value in 2010 minus that in 2012) to be a marker standing for renal function changes at earlier stage of follow-up.

All statistical tests were carried out at a two-tailed significance level of 0.05 using SPSS software version 22 (IBM SPSS Inc., Armonk, NY, USA). The Kruskal-Wallis H test and Pearson Chi-square test were used for univariate analysis as indicated. Cox regression was used for multivariate analysis.

**Results**

Three hundred and twenty patients, including 223 with CKD stage 3a and 97 with CKD 3b, were enrolled in this study. The baseline demographics of the patients at baseline are presented in Table 1. Over half of our patients had albuminuria/proteinuria at baseline (53.3% and 62.7% of patients with CKD stage 3a and 3b, respectively). There were no significant differences in gender, age, BMI, duration of diabetes, percentage of albuminuria/proteinuria, SBP, TC, or LDL at baseline between the patients
with CKD stage 3a and 3b. The patients with CKD stage 3b had more retinopathy (39.2% versus 28.2%, \(P = 0.015\)) and a higher HbA1c at baseline (median 8.2% versus 7.7%, \(P = 0.004\)) than those with CKD stage 3a.

Analyses of the parameters for renal outcomes after 7 years of follow-up are presented in Table 2. After 7 years, 204 (63.7%) cases, including 159 with CKD stage 3a and 45 with CKD 3b, remained at CKD stage 3 while 57 cases (16.6%) had an improvement of CKD stage and 79 cases (24.7%) progressed to CKD stage 4 or 5, including 17 cases (5.3%, 8 males and 9 females) who progressed to dialysis. The cases who had a progression of CKD stage were predominantly female (65.8%) and had a relatively worse eGFR at baseline (in 2010) (median 42.7 ml/min/1.73 m\(^2\)), greater reduction in eGFR in the first 2 years (\(\Delta\text{eGFR/2y median reduction} 2.9 \text{ ml/min/1.73 m}^2\)). These progressive cases also had a higher rate of albuminuria/proteinuria (75.3%) at baseline, longer duration of diabetes (median 13.0 years), higher rate of diabetic retinopathy (50.7%), and higher HbA1c at baseline (median 8.5%) compared to those in the other groups. Moreover, wider fluctuations in the values of HbA1c, SBP, and TC during the 7 years were observed in the progression group (median standard deviation: 1.1% in HbA1c; 17.7 mmHg in SBP; 22.9 mg/dl in TC) (Table 2). The minimum and maximum HbA1c values within the 7-year study period were 5.4% and 11.9% in the CKD 1 + 2 group, 5.0% and 15.0% in the CKD 3a group, 5.9% and 13.8% in the CKD 3b group, and 5.0% and 18.0% in the CKD 4 + 5 group, respectively.

The effects of drug exposure on renal outcomes after 7 years of follow-up are presented in Table 3. The doses of DPP4i, RAASi, SGLT2is, GLP-1RAs and diuretics were prescribed as the optimal dose for the patients with different stages of CKD. The NSAIDs were mostly prescribed as small doses and were seldom used. Significantly more patients who were prescribed with anti-diabetic agents containing SGLT2is had an improvement of CKD stage. There were no significant differences in exposure duration for each drug category, nor the percentages of patients who were prescribed with DPP4is, GLP-1RAs, RAASis, diuretics and NSAIDs between the four groups in the 7 years.

The associated factors for progression or improvement of CKD stage were further analyzed by Cox regression analysis [Tables 4 and 5]. Compared to the cases who remained at CKD stage 3 during the 7-year study period, the associated factors for progression of CKD stage were lower eGFR at baseline (hazard ratio (HR) 0.905, 95% confidence interval (CI) 0.873-0.937, \(P < 0.001\)), greater reduction in eGFR in the first 2 years (HR 1.098, 95% CI 1.063-1.134, \(P < 0.001\)), higher rate of macroalbuminuria/macroproteinuria at baseline (HR 3.268, 95% CI 1.563-6.836, \(P = 0.002\), compared to the patients with normal proteinuria), higher rate of PDR at baseline (HR 1.933, 95% CI 1.043-3.582, \(P = 0.036\), compared to the patients with normal fundus findings), female sex (HR 1.880, 95% CI 1.118-3.159, \(P = 0.017\)), greater variability in the values of HbA1c (HR 1.710, 95% CI 1.007-1.455, \(P = 0.031\)), lower reduction or an increase in eGFR in the first 2 years (HR 0.919, 95% CI 0.888-0.951, \(P < 0.001\)), less variability in the values of HbA1c (HR 0.231, 95% CI 0.068-0.784, \(P = 0.019\)), and the usage of SGLT2is (HR

### Table 1: Baseline demographics

| CKD stage | 3a | 3b | \(P\) |
|-----------|----|----|------|
| \(n\)     | 223| 97 |      |
| eGFR (mL/min/1.73 m\(^2\)) | 53.6 [50.4,56.8] | 40.4 [36.1,43.2] | <0.001 |
| Albuminuria/proteinuria (%) | 53.3 | 62.7 | 0.078 |
| Micro- (%) | 42.9 | 48.9 |      |
| Macro- (%) | 10.4 | 13.8 |      |
| Sex (female) (%) | 51.6 | 58.8 | 0.144 |
| Age (years) | 65.0 [59.0,72.0] | 65.0 [58.0,72.0] | 0.951 |
| Diabetes duration (years) | 11.0 [6.0,15.0] | 11.0 [8.0,15.5] | 0.327 |
| BMI (kg/m\(^2\)) | 26.0 [23.9,28.1] | 25.8 [23.6,28.7] | 0.887 |
| Retinopathy (%) | 28.2 | 39.2 | 0.015 |
| NPDR (%) | 17 | 15.5 |      |
| PDR (%) | 11.2 | 23.7 |      |
| HbA1c (%) | 7.7 [6.9,8.9] | 8.2 [7.2,9.2] | 0.004 |
| SBP (mmHg) | 141.0 [128.0,156.0] | 138.0 [126.0,157.5] | 0.716 |
| TC (mg/dL) | 160.0 [144.0,180.0] | 162.0 [143.0,178.0] | 0.816 |
| LDL (mg/dL) | 97.0 [80.0,117.0] | 94.0 [79.0,115.5] | 0.793 |

Data are median [25\(^{th}\), 75\(^{th}\) percentile] or percentage as indicated. The Kruskal-Wallis H test and Pearson Chi-square test were used for univariate analysis as indicated. CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; BMI: Body mass index; NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; HbA1c: Glycated hemoglobin; SBP: Systolic blood pressure; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol.
This study identified several independent factors relating to renal function in patients with type 2 diabetes and CKD stage 3 in this 7-year longitudinal follow-up. The factors associated with progressive renal impairment included a lower baseline eGFR, greater deterioration in eGFR in the first 2 years, the existence of macroalbuminuria, PDR, wider fluctuations in both HbA1c level and SBP, and female sex. The factors associated with improvements in eGFR included a relatively higher baseline eGFR (i.e. Stage 3a relative to 3b), an increase in eGFR in the first 2 years, and less variability in HbA1c.

Among the factors associated with a progression of diabetic kidney disease, hyperglycemia and hypertension are thought to be the two most prominent factors.\(^5\) In addition, increased variation in SBP has been reported to be positively correlated with impaired renal function in patients with hypertension and to be an independent predictor of the progression of renal damage.\(^12,13\) Experimental data have demonstrated that shear stress caused by oscillations in SBP can result in the initiation and progression of atherosclerosis and the impairment of renal function.\(^13\) In addition, glycemic fluctuation has been reported to increase the risk of endothelial damage, oxidative stress, inflammation and

### Discussion

This study identified several independent factors relating to renal function in patients with type 2 diabetes and CKD stage 3 in this 7-year longitudinal follow-up. The factors associated with progressive renal impairment included a lower baseline eGFR, greater deterioration in eGFR in the first 2 years, the existence of macroalbuminuria, PDR, wider fluctuations in both HbA1c level and SBP, and female sex. The factors associated with improvements in eGFR included a relatively higher baseline eGFR (i.e. Stage 3a relative to 3b), an increase in eGFR in the first 2 years, and less variability in HbA1c.

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### Table 2: Analyses of the parameters for renal outcomes after 7 years of follow-up

| CKD stage after 7 years | 1+2 | 3a | 3b | 4+5 | P |
|------------------------|-----|----|----|-----|---|
| n                      | 37  | 159| 45 | 79  |   |
| Age (years)            | 61.0 [58.0,72.5] | 67.0 [59.0,72.0] | 67.0 [59.0,73.5] | 65.0 [59.0,72.0] | 0.494 |
| Sex (female) (%)       | 45.9 | 49.7| 53.3| 65.8 | 0.041 |
| Diabetes duration (years) | 9.0 [3.0,15.0] | 10.0 [6.0,15.0] | 11.0 [7.0,17.0] | 13.0 [9.0,18.0] | 0.021 |
| Albuminuria/proteinuria (%) | 38.9 | 51.7| 52.3| 75.3 | <0.001 |
| Retinopathy (%)        | 24.3 | 27.0| 22.2| 50.7 | <0.001 |
| NPDR (%)               | 18.9 | 16.3| 11.1| 20.3 |   |
| PDR (%)                | 5.4  | 10.7| 11.1| 30.4 |   |
| eGFR (mL/min/1.73 m²)  |     |     |     |     |   |
| Baseline               | 53.7 [50.2,57.2] | 53.6 [50.3,56.8] | 42.0 [38.5,43.8] | 42.7 [37.7,52.2] | <0.001 |
| At 7th y               | 67.4 [64.9,72.3] | 45.6 [38.5,51.8] | 41.0 [36.3,48.8] | 20.5 [11.1,26.6] | <0.001 |
| ΔeGFR/2y               | -8.4 [-20.8,-2.0] | -2.3 [-6.6,3.0] | -3.6 [-6.3,0.4] | 2.9 [-1.2,9.1] | <0.001 |
| HbA1c at 7 years (%)   |     |     |     |     |   |
| Baseline               | 7.2 [6.8,8.5] | 7.7 [6.9,8.7] | 8.1 [7.2,9.1] | 8.5 [7.1,9.6] | 0.013 |
| Mean                   | 7.6 [7.1,8.4] | 7.9 [7.2,8.6] | 7.8 [7.2,9.3] | 8.2 [7.7,9.0] | 0.059 |
| SD                     | 0.7 [0.5,0.8] | 0.7 [0.5,1.2] | 0.9 [0.6,1.3] | 1.1 [0.7,1.4] | <0.001 |
| SBP (mmHg)             |     |     |     |     |   |
| Baseline               | 133.0 [126.5,154.0] | 141.0 [130.0,155.0] | 140.0 [126.0,155.0] | 140.0 [126.0,163.0] | 0.767 |
| Mean                   | 140.9 [131.8,147.5] | 140.6 [132.4,148.3] | 136.9 [130.9,146.4] | 141.1 [134.4,150.6] | 0.118 |
| SD                     | 17.5 [11.9,21.3] | 14.5 [11.4,19.1] | 16.2 [13.0,20.1] | 17.7 [14.2,22.1] | 0.007 |
| BMI (kg/m²)            |     |     |     |     |   |
| Baseline               | 25.2 [23.4,28.1] | 26.1 [23.4,28.3] | 25.8 [22.9,28.6] | 26.1 [24.3,28.6] | 0.750 |
| Mean                   | 25.6 [23.2,27.7] | 25.9 [23.3,27.8] | 25.7 [22.4,28.0] | 25.8 [23.9,28.5] | 0.755 |
| SD                     | 0.6 [0.4,0.9] | 0.8 [0.5,1.1] | 0.7 [0.5,1.1] | 0.8 [0.6,1.2] | 0.193 |
| TC (mg/dL)             |     |     |     |     |   |
| Baseline               | 168.5 [152.3,190.8] | 159.0 [143.0,178.0] | 166.0 [145.5,184.3] | 159.5 [141.0,178.0] | 0.137 |
| Mean                   | 160.0 [147.3,175.9] | 157.0 [143.8,170.3] | 156.8 [146.6,175.9] | 164.5 [147.7,178.0] | 0.209 |
| SD                     | 19.2 [14.3,27.2] | 17.1 [12.5,24.7] | 21.4 [14.6,28.1] | 22.9 [14.7,31.3] | 0.009 |
| LDL-C (mg/dL)          |     |     |     |     |   |
| Baseline               | 101.0 [82.5,121.3] | 97.0 [79.8,116.0] | 95.0 [79.5,123.0] | 93.0 [78.3,110.0] | 0.472 |
| Mean                   | 93.9 [78.5,100.7] | 86.6 [74.7,102.7] | 89.0 [74.8,105.4] | 92.5 [79.0,100.6] | 0.715 |
| SD                     | 17.3 [12.7,22.9] | 15.0 [9.2,22.8] | 15.6 [11.5,26.2] | 18.2 [11.9,26.3] | 0.066 |

At the end of the 7-year study period, the patients were classified into four groups according to their CKD stages defined as the Modification of Diet in Renal Disease (MDRD). Data are median [25 th, 75 th percentile] or percentage as indicated. The Kruskal-Wallis H test and Pearson Chi-square test were used for univariate analysis as indicated. CKD: Chronic kidney disease; NPDR: non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; eGFR: Estimated glomerular filtration rate; ΔeGFR/2y: Change in eGFR in the first 2 years (the value in 2010 minus that in 2012); HbA1c: Glycated hemoglobin; SBP: Systolic blood pressure; BMI: Body mass index; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; SD: Standard deviation for variation of factors.
end-organ dysfunction.\[14\] One previous study reported that wider perioperative glycemic fluctuations increased the risk of acute kidney injury in both subjects with and without diabetes.\[15\] Our study supports the independent associations of wider fluctuations in both A1c level and systolic blood pressure with the progression of diabetic kidney disease. In contrast, in the 11.7% of patients who had regression of CKD stage after 7 years, less variation in HbA1c seemed to be associated with the improvement in renal function. A previous non-randomized trial reported that the impact of glycemic variability on the progression of CKD was less obvious in patients with advanced CKD stage.\[16\] We also found an association between less variability in HbA1c and a lower risk of progressive renal outcomes in our diabetic patients with early CKD stage 3. However, it is important to remember that an improvement in eGFR cannot be extrapolated into an improvement in renal pathology, for which proof from a biopsy would be required.

Incretin-based diabetes therapies consist of GLP-1RAs and DPP-4is. Reductions in albuminuria were observed in the LEADER, SUSTAIN-6, and SAVOR-TIMI trials.\[17,19\] However, no major benefits on hard renal outcomes (including reduction in doubling of serum creatinine or end-stage renal disease or death due to renal disease) were achieved in these trials.\[17-19\] Nevertheless, a small but statistically significantly lower decline in eGFR was observed with liraglutide compared to a placebo in the LEADER trial, especially in the subgroup with CKD stage 3.\[20\] The effects of DPP4is and GLP-1RAs on the change in CKD stage were statistically insignificant in our study.

SGLT2i have been associated with reductions in the progression of albuminuria in patients with type 2 diabetes.\[21,22\] Despite the initially acute decline in eGFR, trials with SGLT2is (canagliflozin and empagliflozin) have shown better preservation of eGFR during long-term administration than with comparators.\[21,22\] In the EMPA-REG OUTCOME trial, eGFR was statistically higher (4.7 mL/min/1.73 m²) in the group who received empagliflozin after 3.5 years of treatment.\[21\] A slowing of the decline in eGFR was also seen in the subgroup of patients with baseline eGFR below 60 mL/min/1.73 m².\[22\] Although the patients who were prescribed with anti-diabetic agents containing SGLT2is showed significant improvements in CKD stage in our study, the number of cases was small. Further studies with larger series of SGLT2i user will be needed for the conclusion. Yamanouchi M et al. reported that nonproteinuric diabetic patients with eGFR <60 mL/min/1.73 m² had better-controlled blood pressure and were at a lower risk of CKD progression and all-cause mortality compared to propensity score-matched patients with proteinuria.\[7\] In our study, the diabetic patients with eGFR between 45-60 mL/min/1.73 m² in the absence of albuminuria/proteinuria also had a lower risk of CKD progression compared to the other patients. Since eGFR between 45-60 mL/min/1.73 m² in the absence of albuminuria/proteinuria may be related to aging more than kidney disease, the role of age on eGFR should be considered and analyzed.\[21\]

A lower eGFR at diagnosis and older age have been reported to be independently associated with dialysis initiation using Cox regression in patients with CKD stage 3-5.\[24\] Our results also supported the role of lower baseline eGFR on CKD progression in patients with type 2 diabetes and CKD stage 3 in Cox regression analysis. However, age was not significantly associated with CKD progression in Cox regression analysis in this study. It has been demonstrated that the presence of diabetic microangiopathies (such as proteinuria and retinopathy) significantly predict the progression of CKD.\[27\] The CKD progression rates have been reported to be 17.0, 61.4, 130.5, and 295.1 per 1000 person-years in diabetic patients with normal, mildly increased, moderately increased, and severely increased albuminuria at baseline, respectively.\[8\] A significantly higher risk of CKD progression has also been observed in patients with PDR (OR 2.18, 95% CI 1.71–2.78) compared to patients with NPDR.\[9\] Our results support the independent roles of proteinuria/albuminuria and PDR on predicting the progression of CKD stage in patients with stage 3 CKD.

We also found that female sex was an independent factor for the progression of diabetic kidney disease in patients with type 2 diabetes and CKD stage 3. The pooled adjusted relative risk ratio for end-stage renal disease in a previous meta-analysis was

Table 3: The effects of drug exposure on renal outcomes after 7 years of follow-up

| CKD stage after 7 years | 1+2 | 3a | 3b | 4+5 | P  |
|------------------------|-----|----|----|-----|----|
| n                      | 37  | 159| 45 | 79  |    |
| DPP4i                  |     |    |    |     |    |
| %                      | 54.1| 67.9|62.2|75.9 |0.102|
| Mean months            | 58.8| 61.4|60.8|63.3 |0.105|
| RAASI                  |     |    |    |     |    |
| %                      | 89.2| 83.0|91.1|89.9 |0.323|
| Mean months            | 76.2| 74.2|70.0|72.9 |0.245|
| Diuretic               |     |    |    |     |    |
| %                      | 29.7| 24.5|28.9|34.2 |0.474|
| Mean months            | 39.5| 57.5|58.1|55.9 |0.104|
| SGLT2i                 |     |    |    |     |    |
| %                      | 13.5| 2.5 |2.2 |1.3  |0.009|
| Mean months            | 14.2| 14.8|13.0|13.0 |0.112|
| GLP-1RA                |     |    |    |     |    |
| %                      | 0   | 3.1 |2.2 |2.5  |0.745|
| Mean months            | 0   | 27.6|14.0|40.0 |0.761|
| NSAID                  |     |    |    |     |    |
| %                      | 59.5| 36.5|48.9|42.3 |0.058|
| Mean days              | 134.1|193.1|151.5|120.2|0.331|

At the end of the 7-year study period, the patients were classified into four groups according to their CKD stages defined as the Modification of Diet in Renal Disease (MDRD). The effect of each drug exposure was presented as the duration and percentage of exposure of that drug. The use of NSAIDs was defined as exposure for any duration and presented as days of exposure, while the use of other medications was defined as exposure to the specific classification of medication for any duration during the 7 years of this study and presented as months of exposure.

CKD: Chronic kidney disease; DPP4i: Dipeptidyl peptidase 4 inhibitor; RAASI: Renin-angiotensin-aldosterone system inhibitor; SGLT2i: Sodium-glucose cotransporter 2 inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; NSAID: Non-steroidal anti-inflammatory drug
Table 4: Factor analysis for progression in CKD stage after 7 years

| Factor                        | Univariate HR (95% CI) | P  | Multivariate HR (95% CI) | P  |
|-------------------------------|------------------------|----|--------------------------|----|
| eGFR at baseline              | 0.909 (0.884-0.935)    | <0.001 | 0.905 (0.873-0.937)    | <0.001 |
| ΔeGFR/2y                      | 1.091 (1.060-1.122)    | <0.001 | 1.098 (1.063-1.134)    | <0.001 |
| Albuminuria/proteinuria at baseline | <0.001                  |    | <0.001                  |    |
| Micro                         | 1.980 (1.144-3.427)    | 0.015 | 1.535 (0.839-2.808)    | 0.164 |
| Macro                         | 4.506 (2.382-8.523)    | <0.001 | 3.268 (1.563-6.836)    | 0.002 |
| Retinopathy at baseline       | <0.001                  |    | <0.001                  |    |
| NPDR                          | 1.893 (1.011-3.546)    | 0.046 | 1.797 (0.858-3.766)    | 0.120 |
| PDR                           | 3.381 (1.929-5.928)    | <0.001 | 1.933 (1.043-3.582)    | 0.036 |
| Age                           | 0.992 (0.969-1.015)    | 0.485 | 0.999 (0.969-1.029)    | 0.921 |
| Sex (female)                  | 1.748 (1.098-2.783)    | 0.019 | 1.880 (1.118-3.159)    | 0.017 |
| HbA1c at baseline             | 1.254 (1.099-1.431)    | 0.001 | 0.986 (0.830-1.171)    | 0.869 |
| HbA1c SD at 7 years           | 2.108 (1.453-3.057)    | <0.001 | 1.710 (1.033-2.832)    | 0.037 |
| SBP SD at 7 years             | 1.046 (1.012-1.082)    | 0.008 | 1.052 (1.008-1.097)    | 0.019 |
| TC SD at 7 years              | 1.021 (1.007-1.037)    | 0.005 | 1.006 (0.988-1.025)    | 0.489 |
| SGLT2i use                    | 0.444 (0.062-3.194)    | 0.420 | 1.146 (0.149-8.818)    | 0.896 |

At the end of the 7-year study period, study parameters of patients with eGFR < 30 mL/min/1.73m² were compared to that of patients with eGFR between 60 and 30 mL/min/1.73m². CKD: chronic kidney disease; eGFR: Estimated glomerular filtration rate; ΔeGFR/2y: Change in eGFR in the first 2 years (the value in 2010 minus that in 2012); NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; HbA1c: Glycated hemoglobin; SD: Standard deviation for variation of factors; SBP: Systolic blood pressure; TC: Total cholesterol; SGLT2i: Sodium glucose cotransporter 2 inhibitor

Table 5: Factor analysis for improvement in CKD stage after 7 years

| Factor                        | Univariate HR (95% CI) | P  | Multivariate HR (95% CI) | P  |
|-------------------------------|------------------------|----|--------------------------|----|
| eGFR at baseline              | 1.053 (0.995-1.114)    | 0.072 | 1.074 (1.007-1.145)    | 0.031 |
| ΔeGFR/2y                      | 0.943 (0.920-0.966)    | <0.001 | 0.919 (0.888-0.951)    | <0.001 |
| Albuminuria/proteinuria at baseline | 0.317                  |    | 0.592                  |    |
| Micro                         | 0.681 (0.343-1.351)    | 0.271 | 0.737 (0.307-1.770)    | 0.495 |
| Macro                         | 0.301 (0.041-2.232)    | 0.240 | 0.385 (0.046-3.224)    | 0.378 |
| Retinopathy at baseline       | 0.584                  |    | 0.948                  |    |
| NPDR                          | 1.080 (0.459-2.541)    | 0.859 | 1.247 (0.435-3.575)    | 0.681 |
| PDR                           | 0.461 (0.108-1.967)    | 0.296 | 0.959 (0.204-4.510)    | 0.958 |
| Age                           | 0.983 (0.950-1.017)    | 0.315 | 0.996 (0.951-1.044)    | 0.869 |
| Sex (female)                  | 0.845 (0.442-1.613)    | 0.617 | 0.550 (0.244-1.243)    | 0.151 |
| HbA1c at baseline             | 0.844 (0.650-1.095)    | 0.202 | 1.050 (0.740-1.489)    | 0.784 |
| HbA1c SD at 7 years           | 0.334 (0.137-0.810)    | 0.015 | 0.231 (0.068-0.784)    | 0.019 |
| SBP SD at 7 years             | 1.022 (0.972-1.074)    | 0.391 | 1.017 (0.964-1.073)    | 0.536 |
| TC SD at 7 years              | 1.006 (0.978-1.035)    | 0.673 | 1.028 (0.988-1.069)    | 0.169 |
| SGLT2i use                    | 3.772 (1.469-9.686)    | 0.006 | 5.150 (1.353-19.601)   | 0.016 |

At the end of the 7-year study period, study parameters of patients with eGFR > 60 mL/min/1.73m² were compared to that of patients with eGFR between 60 and 30 mL/min/1.73m². CKD: chronic kidney disease; eGFR: Estimated glomerular filtration rate; ΔeGFR/2y: Change in eGFR in the first 2 years (the value in 2010 minus that in 2012); NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; HbA1c: Glycated hemoglobin; SD: Standard deviation for variation of factors; SBP: Systolic blood pressure; TC: Total cholesterol; SGLT2i: Sodium glucose cotransporter 2 inhibitor

38% higher in women with diabetes than in men with diabetes, indicating that female sex may accelerate the progression of diabetic kidney disease, which is consistent with our findings. Evidence from large trials has demonstrated the significant renal protective effect of RAASIs through reducing albuminuria in patients with diabetes. However, benefits in slowing the decline in renal function has not been demonstrated with RAASIs. In this study, more than 80% of our patients received RAASIs, and there was no statistically significant difference in their administration among the 3 groups. Although NSAIDs are known to be a potentially nephrotoxic agent, the association between NSAIDs and changes in CKD stage was insignificant. This may be explained by the infrequent use of NSAIDs in this study. This study is limited by the small number of cases, the lack of information on the amount of protein in their diet, and a lack of information on home blood pressure monitoring or 24-hour blood pressure monitoring. Besides, some biomarkers,
such as cystatin C, neutrophil gelatinase-associated lipocalin, fibroblast growth factor-21, the symmetric to asymmetric dimethylarginine ratio, β2-microglobulin, C16-acylcarnitine, or kidney injury molecule-1 were not provided in this study.[24] Nevertheless, the share-care system provides appropriate and validated treatment and information for this long-term study and comprehensive analysis.[11]

In conclusion, for patients with type 2 diabetes and CKD stage 3 in this study, lower eGFR, large fluctuations in HbA1c, SBP, and the presence of macroalbuminuria and PDR at baseline were significant predictors for the progression of CKD in as short as 7 years. On the contrary, less fluctuations in HbA1c and improvements in eGFR as early as possible were associated with better long-term renal outcomes in patients with type 2 diabetes and CKD stage 3. However, further research is necessary to see if attenuation of blood sugar and blood pressure variations will be renoprotective.

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