Original Article

Prevalence and Predictors of Glomerular Filtration Rate Decline in Patients with Diabetic Kidney Disease Using RAAS Blocking Agents

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Background: Diabetes conduces to an increased risk of deteriorating renal impairment. Renin-angiotensin-aldosterone system (RAAS) blocking agents were used to preserve renal progression among type 2 diabetes mellitus (DM) patients. However, rapid estimated glomerular filtration rate (eGFR) decline was still presented.

Objective: The present study is to identify the risk factors for rapid eGFR decline among type 2 DM patients using RAAS blocking agents, and to evaluate the impacts of RAAS blocking agents in inappropriate administration to renal events, cerebrovascular events, and coronary events.

Materials and Methods: The present study was a retrospective 2-year period study between 2016 and 2017. Patients with type 2 diabetes were treated with RAAS blocking agents. Multivariate logistic regression was used to access the risk factors of the rapid eGFR decline compared with non-rapid eGFR decline. Relative risk was obtained to evaluate the renal outcome between appropriate use of RAAS blocking agents compared with inappropriate usage.

Results: Of the total 500 patients, 195 subjects developed rapidly decreased eGFR of more than 5 mL/minute/1.73 m^2 over one year. Predictive factors significantly associated with rapid decline eGFR were cardiovascular disease (adjusted odds ratio [OR] 6.59; p=0.020), urine albumin creatinine ratio of more than 1000 mg/g (adjusted OR 3.31; p=0.017), and normoalbuminemia (adjusted OR 0.44; p=0.011). There was the significant association with the risk of persistent albuminuria in patients who received inappropriate RAAS blocking agents compared with patients who received appropriate RAAS blocking agents (RR 1.23; 95% CI 1.06 to 1.43).

Conclusion: Cardiovascular disease, albuminuria, and hypoalbuminemia are the major risk factors leading to rapid decline eGFR developing in type 2 DM patients who received RAAS blocking agents. Moreover, the appropriate use of RAAS blocking agents should be a concerned issue.

Keywords: Diabetic kidney disease, RAAS blocking agents, Albuminuria

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Diabetes represents the most common cause of chronic renal failure and end-stage renal disease (ESRD) in Thailand. Diabetes was the etiology of ESRD in 38% to 40% between 2007 and 2015[(1)]. Diabetic kidney disease (DKD) is a complication of diabetes mellitus (DM). Patients with DKD are characterized by the occurrence of increased levels of urinary albumin excretion of more than 30 mg/g (microalbuminuria). Renin-angiotensin-aldosterone system (RAAS) blocking agents impair the estimated glomerular filtration rate (eGFR) or both[(2)]. Without specific medication and interventions, microalbuminuria progresses to the other stage of diabetic nephropathy (macroalbuminuria), which is

defined by urinary albumin excretion of more than 300 mg/g. Most DKD progresses and continues to a rapid decline in renal function, which may lead to chronic renal failure within months. National and international guidelines have recommended that RAAS blocking agent should be first-line medication in patients with DKD to diminish albuminuria and delay the progression of renal failure[3-5]. Much awareness has been given to secondary prevention strategies for patients with DKD by attempting to retard the progression of microalbuminuria and macroalbuminuria to ESRD[6]. However, RAAS blocking agents are not recommended in DM patients with greater glomerular filtration rate (GFR) decline.

The use of RAAS blocking agent is preferred in patients with DKD as these drugs show cardiovascular and renal protection beyond blood pressure reduction compared with other antihypertensive drug classes. The IRMA 2, BENEDICT, INNOVATION, and ROADMAP studies showed that RAAS blocking agents can prevent transition from normoalbuminuria to microalbuminuria, as well as from microalbumiuria to macroalbuminuria in hypertensive diabetic patients[7-11]. RAAS blocking agents are not able to prevent the development of microalbuminuria in normotensive individuals with type 2 diabetes. Whether RAAS blocking agents have an effect over and above blood pressure control in decreasing the rate of chronic kidney disease (CKD) progression in those without increased urine albumin excretion rate is uncertain. However, most DM patients using RAAS blocking agents still have rapid eGFR decline. The relative risk factors of the rapid eGFR declined (of more than 5 mL/minute/1.73 m^2 per year) in DKD patients are not well defined. Furthermore, potential causes accounting for variation in DKD and its rate of progression after RAAS blocking agent are still largely unexplored. For example, acute kidney injury (AKI) is usually diagnosed by rapid decrease in renal function over a relatively transient period of time. Other risk factors for AKI include the use of medications that alter renal blood flow and intrarenal hemodynamics, the use of medications that cause kidney injury (e.g., non-steroidal anti-inflammatory drugs), and preexisting CKD. Many antihypertensive medications (e.g., angiotensin-converting-enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], and diuretics) can reduce intravascular volume, renal blood flow, or glomerular filtration[12]. There is a concern that sodium-glucose cotransporter 2 (SGLT2) inhibitors may aggravate volume depletion and subsequent AKI, particularly when combined with RAAS block that reduces glomerular filtration[13-15].

According to Clinical Practice Recommendation for the Evaluation and Management of CKD in Adults 2015, RAAS blocking agents should be recommended based on levels of blood pressure and albuminuria. In practice, RAAS blocking agent usages are mostly not followed to the clinical practice guideline; doses of RAAS blocking agents were not adjusted in patients with systolic blood pressure of more than 130 mmHg or less than 110 mmHg. Furthermore, the effect of appropriate RAAS blocking agent use to renal and cardiovascular outcomes have not been investigated among Thai type 2 DM patients.

The present study wanted to evaluate the predictor factors for rapid eGFR decline among type 2 DM patients using RAAS blocking agents and impact of RAAS blocking agents in inappropriate administration to renal events, cerebrovascular events, and coronary events.

Materials and Methods

Study population and sample sizes

A retrospective 2-year study was performed to identify the prevalence and the predictors of eGFR Rate Decline in Patients with type 2 diabetics using RAAS blocking agents at the Taksin Hospital, Bangkok Metropolitan Administration, Thailand. The data were retrieved and collected from the electronic program between 1 January 2016 and 31 December 2017. Patients were recruited if they had type 2 DM, received ACEIs or ARBs or both, and were 18 years old or older. Patients were excluded if they were younger than 18 years old, pregnant, type 1 DM, or if they had a history of cancer, autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), a history of other renal disease, or previous renal function disorders (i.e., polycystic kidney disease, acute renal failure, glomerulonephritis, kidney stone, or hematuria). The patients were also excluded if the eGFR measurements were performed less than two times.

The sample size was calculated based on the prevalence of GFR decline in patients with DKD using RAAS blocking agents, which was at 18% in the previous study[10]. With the power of a 2-sided test at the 0.05 level of significance, 500 evaluable diabetic kidney patients were needed to obtain a result.

The measurement of risk factors

Demographic data and physical examinations (i.e., gender, age, smoking status, weight, height) were collected by the nurses. Body mass index

(BMI) was calculated by weight (kg) divided by squared height (m^2). Blood pressure was measured by a nurse after resting at least five minutes. Blood tests (i.e., HbA1c, low density lipoprotein cholesterol [LDL], high density lipoprotein cholesterol [HDL], triglyceride [TG], total cholesterol, uric acid, fasting serum glucose concentration serum creatinine, serum albumin, urine albumin, and eGFR) were collected from 8-hour overnight fasting blood samples. The eGFR estimate was calculated from serum creatinine using a validated formula. The CKD Epidemiology Collaboration (CKD-EPI) equation was performed[4]. Albumin-to-creatinine ratio (ACR) were collected from the urine test. Definite clinical events including non-fatal myocardial infarction, angina pectoris, and cerebrovascular disease were collected based on the ICD-10 code I25.9, I20.9, I21, I63.9. The medication therapy was collected from the medical record. Appropriately used RAAS blocking agents were defined as using RAAS blocking agents with the effective dose that can control blood pressure to the target, which is less than 130 over 80 mmHg or the dose of RAAS block agents were not associated with unacceptable side effects such as hypotension, acute renal failure, hyperkalemia, or uncontrolled cough.

The definitions of outcomes

The primary outcome was rapidly worsening of eGFR defined as decrease of eGFR of more than 5 mL/minute/1.73 m^2[2-4]. The secondary outcomes included total renal events, new or worsen nephropathy, new-onset persistent microalbuminuria, total cerebrovascular, and total coronary event. The total renal events were defined as the presenting of ESRD, sustained estimated eGFR of less than 15 mL/minute/1.73 m^2 for at least 30 days, doubling of the serum creatinine level from baseline, or need for renal replacement therapy. The new or worsened nephropathy was defined as a progression of albuminuria to more than 30% persistent for at least 30 days, changing from either non-albuminuria to microalbuminuria, or from microalbuminuria to macroalbuminuria. The persistent albuminuria was defined as the ratio of albumin to creatinine of more than 30 mg/g during two years of study. The total cerebrovascular event was defined as ischemic or hemorrhagic cerebral infarction, and the total coronary event was defined as non-fatal myocardial infarction or angina pectoris.

Statistical analysis

To analyze for variance of the baseline characteristics, categorical variables were assessed by chi-square test, and continuous variables were assessed by Student t-test or Mann-Whitney-U test. Multiple logistic regression analyses were performed to evaluate risk factors of rapid decline eGFR. Relative risk was obtained to find the association between RAAS blocking agents using and total renal events.

Stata Statistical Software, version 16.0 (StataCorp LLC, College Station, TX, USA) was used for the analyses. The risk estimates of predictor factors in rapid decline eGFR were presented as odd ratio and 95% confidence interval. A p-value of less than 0.05 was considered as statistically significant.

Ethical approval

The present study had been approved by the Bangkok Metropolitan Administration's Ethics Committee (S013h/60_EXP).

Results

The present investigation was a single-center retrospective cohort study in Taksin Hospital. All patients with type 2 DM from nephrology and diabetes center using RAAS blocking agents were enrolled. The baseline characteristics and results by univariate analysis of 500 diabetes patients with rapid decline eGFR group compared to those in the non-rapid decline eGFR group were shown in Table 1. Forty percent of them were male and the mean age was 63.77±11.49 years. Among these patients, 16.81% had a history of smoking. The mean BMI was 27.33 kg/m^2 and morbid obesity (BMI more than 30 kg/m^2) was seen in 28.40%. They were separated into two groups, rapid decline eGFR and non-rapid decline eGFR. One hundred ninety-five (39%) patients developed to rapidly decreased eGFR of more than 5 mL/minute/1.73m^2 over one year. A higher level of urinary ACR (746.37 versus 281.68 mg/g; p=0.017) and lower level of serum albumin (3.94 versus 4.22 mg/dl; p<0.001) were significantly associated with rapid decline eGFR.

Comparison between the patients with rapid decline eGFR and non-rapid decline eGFR groups revealed that diabetic patients with rapid decline eGFR had significant prevalence of myocardial infarction (8.21% versus 1.97%; p=0.001), angina pectoris (10% versus 2%; p=0.001), and doubling of the serum creatinine level (12.82% versus 2.62%; p<0.001) as shown in Table 2. No significant statistical difference in any combination of medication

Table 1. Baseline characteristics of patients with diabetic kidney disease, rapid decline eGFR group, and non-rapid decline eGFR group

	Total Mean±SD	Rapid decline eGFR[+] Mean±SD	Non-rapid decline eGFR[#] Mean±SD	p-value
Number of patients; n (%)	500 (100)	195 (39.00)	305 (61.00)	
Age (year)	63.77±11.49	63.97±11.80	63.47±11.01	0.630
Sex: male; n (%)	201 (40.20)	81 (41.54)	120 (39.34)	0.625
Smoking habit; n (%)	49 (16.81)	16 (18.39)	24 (15.89)	0.620
Non-smoke; n (%)	198 (83.19)	81 (81.61)	127 (84.11)	0.620
BMI (kg/m^2)*	27.33±5.23	26.96±5.31	27.57±5.18	0.191
BMI >30*; n (%)	142 (28.40)	55 (28.21)	87 (28.52)	0.938
BMI ≥25*; n (%)	326 (65.20)	121 (62.05)	205 (67.21)	0.237
HbA1c (mg%)[†]	7.97±1.98	8.17±2.22	7.84±1.79	0.196
Fasting serum glucose concentration (mg/dL)	166.60±52.85	171.34±58.48	163.57±48.80	0.471
LDL (mg/dl)	107.29±31.82	109.26±33.80	106.06±30.50	0.422
HDL mg/dl)	50.14±12.13	49.1±111.74	50.79±12.34	0.117
TG (mg/dl)	168.50±120.76	172.13±138.04	166.22±108.71	0.635
Total cholesterol (mg/dl)	193.37±46.11	195.55±49.54	192.01±43.85	0.742
Uric acid (mg/dl)	6.61±1.97	6.56±2.06	6.64±1.92	0.498
Creatinine (mg/dl)	1.19±0.43	1.19±0.45	1.19±0.43	0.661
Urinary ACR (mg/g)[‡]	444.64±1,284.99	746.36±1,801.03	281.68±851.50	0.017
Serum albumin (mg/dl)	4.11±0.54	3.94±0.59	4.22±0.47	<0.001
eGFR (mL/minute/1.73 m^2)	62.03±23.56	62.40±22.74	61.79±24.11	0.500
Systolic blood pressure (mmHg)	141.89±15.14	142.28±15.82	141.64±14.71	0.870
Diastolic blood pressure (mmHg)	73.45±7.61	73.21±7.65	73.59±7.59	0.623

eGFR=estimated glomerular filtration rate; SD=standard deviation; BMI=body mass index; LDL=low density lipoprotein cholesterol; HDL=high density lipoprotein cholesterol; TG=triglyceride; ACR=albumin-to-creatinine ratio

* BMI is the weight in kilograms divided by the square of the height in meters, [†] HbA1c adjusted glycated hemoglobin, [‡] Urinary ACR from a spot urine collection was calculated with albumin measured in milligrams and creatinine measured in grams, [+] Decline eGFR >5 mL/minute/1.73 m^2 per year, [#] Decline eGFR ≤5 mL/minute/1.73 m^2 per year

Table 2. Underlying medical conditions and medical complications of patients with diabetic kidney disease between rapid decline eGFR and non-rapid decline eGFR groups

	Total n (%)	Rapid decline n (%)	Non-rapid n (%)	p-value
Acute stroke	59 (11.80)	22 (11.28)	37 (12.13)	0.774
CVD	90 (18.00)	40 (20.51)	50 (16.39)	0.242
MI	22 (4.40)	16 (8.21)	6 (1.97)	0.001
Angina pectoris	12 (2.40)	10 (5.13)	2 (0.66)	0.001
Doubling Scr	33 (6.60)	25 (12.82)	8 (2.62)	<0.001

CVD=cardiovascular disease and cerebrovascular disease; MI=myocardial infarction; Doubling Scr=doubling of the serum creatinine level

with RAAS blocking agents were found in rapid decline eGFR comparing with non-rapid decline eGFR groups (Table 3). The use of non-steroidal anti-inflammatory drugs (NSAIDs) in DKD patients (28.80%) was commonly identified as drug-disease interaction. The present study found that SGLT2 inhibitors did not significantly influence the rapid decline of eGFR.

Table 4 lists the predictor factors associated with rapid decline eGFR in DKD. All the possible

Table 3. Drugs use in patients with diabetic kidney disease between rapid decline eGFR and non-rapid decline eGFR groups

Drug	Total n (%)	Rapid decline n (%)	Non-rapid n (%)	p-value
Insulins	199 (39.80)	82 (42.05)	117 (38.36)	0.411
Sulfonylureas	319 (63.80)	128 (65.64)	191 (62.62)	0.493
SGLT2 inhibitors	65 (13.00)	26 (13.33)	39 (12.79)	0.859
DPP4 inhibitors	98 (19.60)	41 (21.03)	57 (18.69)	0.521
TZD	179 (3.40)	9 (4.62)	8 (2.62)	0.231
ACEIs	234 (46.80)	93 (47.69)	141 (46.23)	0.749
ARBs	332 (66.40)	132 (67.69)	200 (65.57)	0.625
fibrates	99 (19.80)	45 (23.08)	54 (17.70)	0.625
NSAIDs	144 (28.80)	40 (20.51)	104 (34.10)	0.001
Diuretic	213 (42.60)	86 (44.10)	127 (41.64)	0.587
Metformin	392 (78.40)	151 (77.44)	241 (79.02)	0.675

SGLT2 inhibitors=sodium-glucose cotransporter 2 inhibitors (dapagliflozin, empagliflozin); DPP4 inhibitors=dipeptidyl peptidase-4 inhibitor (sitagliptin, vildagliptin, linagliptin, alogliptin); TZD=thiazolidinedione (pioglitazone); ACEIs=angiotensin-converting-enzyme inhibitors (enalapril, coversyl arginine, or ramipril); ARBs=angiotensin II-receptor blockers (losartan, valsartan, telmisartan, irbesartan, azilsartan, or candesartan); NSAIDs=non-steroidal anti-inflammatory drugs

Table 4. Multivariate logistic regression analysis for rapid decline eGFR among in diabetic kidney disease patients using RAAS blocking agents

Indicator	Adjusted odd ratio	95% confidence interval	p-value
Cardiovascular disease*	6.59	1.35 to 32.26	0.020
urinary ACR >1,000 (mg/g)	3.31	1.23 to 8.88	0.017
Serum albumin†	0.44	0.25 to 0.75	0.011

ACR=albumin-to-creatinine ratio

* Myocardial infarction and angina pectoris, † Serum albumin was the same as or more than 4 mg/dl

variables using logistic regression model analysis to obtain independent risk factors have been listed. Among these variables, cardiovascular disease was a strong independent risk factor of rapid decline eGFR (adjusted odds ratio [OR] 6.59, 95% CI 1.35 to 32.26; p=0.020). The potential risk factors to predict rapid decline eGFR were urinary ACR (adjusted OR 3.31, 95% CI 1.23 to 8.88; p=0.017), and serum albumin (adjusted OR 0.44, 95% CI 0.25 to 0.75; p=0.011).

Analysis of RAAS blocking agents showed that 281 (56.2%) patients received inappropriate RAAS blocking agents and 219 (43.8%) patients received appropriate RAAS blocking agents. Appropriate RAAS blocking agents'treatment significantly reduced the risk of new microalbuminuria. The relative risk of persistent albuminuria was 123% greater in the inappropriate RAAS blocking agents used than in the appropriate used (relative risk 1.23, 95% CI, 1.06 to 1.43, p=0.006) (Table 5).

Discussion

According to the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guidelines, a rapid decline in renal function is defined as a sustained reduction in eGFR of more than 5 mL/minute/1.73 m^2 of body-surface area per year[3]. RAAS blocking agents are the only approved renoprotective medication in type 2 diabetes and are recommended as a first-line medication for DKD with hypertension[3,16-18]. The beneficial effect of treatment DKD is based almost exclusively on the prevention of microalbuminuria and reduction of worsening nephropathy. A meta-analysis that included 26 randomized controlled trials (RCTs) showed that in DKD patients, RAAS blocking agents significantly reduced the risks of doubling of the serum creatinine level by approximately 25%[10]. Evidence for the effect on the rapid decline in eGFR or doubling of the serum creatinine when already treated DKD patients with RAAS blocking agents is limited in the previous

Table 5. Comparison of appropriate and inappropriate RAAS blocking agents is used in diabetic kidney disease by relative risk and conference interval

	Appropiate RAAS	Inappropiate RAAS	RR	95% CI		p-value
				Lower	Upper	
Total renal event	190	245	0.93	0.70	1.15	0.501
New or worsen nephropathy*	15	8	0.93	0.48	1.81	0.843
Persistent albuminuria†	98	146	1.23	1.06	1.43	0.006
Total cerebrovascular event	36	40	0.87	0.57	1.31	0.495
Total coronary event	41	51	0.97	0.67	1.41	0.869

RAAS=renin-angiotensin-aldosterone system; RR=relative risk; CI=conference interval

* New or worsen nephropathy composite of rising of albuminuria more than 30% persistent at least 30 days, change from either normoalbuminuria to microalbuminuria, or from microalbuminuria to macroalbuminuria

† Maintain level of albuminuria that ratio of albumin to creatinine >30 mg/g during study[3-5]

study[15]. In patients with DKD, the apparent cause to be different in the rate of renal function decline is related to the presence of increased urinary albumin excretion rates. In this study, the authors found that patients with DKD who received RAAS blocking agents and rapidly declined eGFR had significantly higher level of urinary albumin excretion rates and lower level of serum albumin. There was a tendency toward higher glycated HbA1c in rapid decline eGFR group but it was not statistically significant[19].

The relationship between DKD and cardiovascular disease remains complex. Cardiovascular disease is associated with both increases in urinary albumin excretion rates and decrease eGFR independent of other cardiovascular disease risk factors[20-22]. The relationship between the presence of microalbuminuria and cardiovascular disease in diabetic individuals has been known for over 25 years[23-25]. However, treatments that affect the progression of CKD may not always have the same effect on the development of the cardiovascular disease. Microalbuminuria approximately doubled the risk of cardiovascular disease. Microalbuminuria may reflect more general damage to the vascular endothelium. Reduced eGFR is a manifestation of systemic atherosclerosis. Chronic activation of RAAS has been implicated in a wide range of cardiovascular diseases, including atherosclerosis, myocardial infarction, and diabetes and its associated comorbidities[26]. When the cardiovascular effects such as myocardial infarction or angina pectoris in patients assigned RAAS blocking agents were assessed in the present trial, rapid decline eGFR was seen over other disease. Then RAAS blocking agents should not be only used to prevent the progression of CKD[18]. Primary multifactorial treatment and interventions aimed at slowing the progression of DKD include combination therapy for diminishing hypertension, controlling hyperglycemia, reduction microalbuminuria, and dyslipidemia.

The population of DKD people is increasing worldwide and most of them face chronic diseases and require several medications for prevention and treatment. They are prone to the risk of medication-related problems such as drug-disease interactions. It is unclear whether any class of oral hypoglycemic drugs and antihypertensive agents combination with RAAS blocking agent are more effective in preventing deterioration of the renal function than the others. Increased awareness of physicians to stop using NSAIDs was conducted by electronic warning in this group. Then, the use of NSAIDs was seen less in rapid decline eGFR group.

The result of a multivariate logistic regression for rapid decline eGFR among type 2 DM patients using RAAS blocking agents showed that type 2 DM patients with myocardial infarction, angina pectoris, and urinary ACR more than 1,000 mg/g had significant risk association of rapid eGFR decline. In addition, normal serum albumin significantly tend to protect DKD patients using RAAS blocking agents from being affected by rapid eGFR decline. As a result, type 2 DM patients with cardiovascular disease and hypoalbuminemia who used RAAS blocking agents should be monitored closely for renal function. Moreover, health care provider should pay attention to the clinical DM seriously, i.e., controlling blood glucose, blood pressure, proteinuria, to prevent renal progression.

Microalbuminuria identifies diabetic individuals at higher risk of overt albuminuria and further of ESRD. It is a good surrogate for ESRD. The present trial of effect of RAAS blocking agent varies with

baseline BP, renal function, and any variability is likely to be quantitative. Inappropriate use of RAAS blocking agents is defined as usage of overdose RAAS blocking agents in normoalbuminuric, normotensive patients, or lower dose of RAAS blockade in persistent hypertension. There is absence of such evidence of RAAS blocking agent lowering the risk of subsequent renal decline in normoalbuminuric, normotensive patients[27].

For the RAAS blocking agents usage, the result showed that inappropriate RAAS blocking agents had significant risk associated to persistent albuminuria as compared with the appropriate RAAS blocking agents. As of the result, healthcare providers should be aware to dispense RAAS blocking agents based on levels of blood pressure and albuminuria.

Conclusion

The progression of DKD is highly variable. Diabetic patients with advanced albuminuria, lower serum albumin, cardiac atherosclerosis, or AKI should consider the risks of a rapid decline in eGFR. Early detection of the risk of advancing CKD with a more aggressive multifactorial approach to renal and cardiovascular protection and ameliorating the risk is important to retard disease progression and reduce complication. Moreover, the appropriate RAAS blocking agents should be a concerned issue.

What is already known on this topic?

1. Renin-angiotensin system blockade is the only approved renoprotective medication in type 2 diabetes with DKD and cardiovascular disease.

2. The associated risk factors among diabetic kidney patients with rapid decline GFR decline are not well defined.

3. RAAS blocking agents are proven to prevent macroalbuminuria and slowly progressing renal failure.

What this study adds?

1. Diabetic patients with advanced albuminuria, lower serum albumin, cardiac atherosclerosis, or AKI should consider the risks of a rapid decline in eGFR. DKD patients with myocardial infarction and angina pectoris should be using RAAS blocking agents with close monitoring. Furthermore, malnutrition should be a concerned issue during treating diabetes patients with RAAS blocking agents.

2. In patients with DKD, in whom using an appropriate dose of RAAS blocking agents have been shown to retard albuminuria, this benefit may not relate to the degree of albuminuria.

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Conflicts of interest

The authors declare no conflict of interest.

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