A Retrospective Cohort Study on Clinical Characteristics, Treatment Patterns, and Disease Outcomes in Chronic Kidney Disease in Patients with Diabetes Using a Japanese Claims Database

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ISPOR 2019, Copenhagen, Denmark, November 2-6 2019. PUK22.

OBJECTIVE

- To characterize clinical characteristics, treatment patterns and outcomes of chronic kidney disease (CKD) in patients with diabetes, using a Japanese claims database with a focus on the use of Mineralocorticoid Receptor Antagonists (MRA) in real-world settings in this population.

METHOD

Study design

- This retrospective cohort study utilized the MDV database, a large, electronic health records-based claims database in Japan.
- The MDV database, which is an electronic health records-based database, comprised of anonymized data from 242 hospitals in Japan; covers approximately 15% of acute phase hospitals and contains data for 13.93 million people as of Dec 2016.
  - The observation period was a maximum of 8 years (from 1st Apr 2008 to 31st Aug 2016).
  - Inclusion criteria were a claim with a diagnosis of diabetes (ICD-10: E10-E14), eGFR less than 60 mL/min/1.73 m^2 at index, and use of any antiglycemic medications within 6 months of the pre-index or index month (Figure 1).

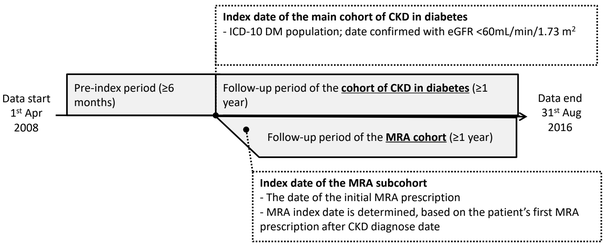

Figure 1. Study design

  - Patients who met any of the following criteria were excluded: those who do not have at least 2 claims within the 1-year follow-up period; those who do not have at least 1 claim within the 6-month pre-index period; or those with a diagnosis of End Stage Renal Disease (ESRD), Polycystic Kidney Disease (PKD), or Immunoglobin Class A (IGA) within the pre-index period.

- The following information was collected from the database
  - demographics (e.g., age, gender)
  - drugs (e.g., brand name, dose, days supply)
  - drug indication
  - diagnoses (e.g., date of diagnosis, ICD-10 diagnosis codes)
  - laboratory tests performed (e.g., HbA1c), and laboratory test results (if available)

- Patients using Angiotensin-Converting Enzyme inhibitor (ACEi), Angiotensin II Receptor Blocker (ARB), MRA, Calcium Channel Blockers (CCB), or combination during the month of the index date/follow-up period were identified based on drug codes
- Outcome event measures were identified from claims with an ICD-10 diagnosis code or other relevant codes
- Most outcomes events are collected anytime in the follow-up period

Statistical Analysis

- Univariate analysis of time-to-event was performed for hyperkalemia, renal, and cardiovascular (CV)-related endpoints
- Cox Proportional Hazards models for hyperkalemia, renal, and CV-related endpoints were conducted to evaluate the effect of eGFR level at baseline on the time to endpoint for the entire cohort and subcohort

Table 1. Patient characteristics at baseline

	CKD in diabetes cohort (N=19,582)		MRA subcohort (N=2,295)	
	Mean	SD	Mean	SD
Age on index date (years)	70.32	10.59	71.54	11.05
Charlson Comorbidity Index	3.00	2.39	3.68	2.38
	n	%	n	%
Gender, n (%)				
Male	11,776	60.14	1,364	59.43
Female	7,806	39.86	931	40.57
Type of diabetes, n (%)				
T1DM (E10)	436	2.23	30	1.31
T2DM (E11)	12,629	64.49	1,659	72.29
Unknown (E12, E13, E14)	11,546	58.96	1,229	53.55
HbA1c at baseline, n (%)				
≤7%	8,946	45.68	976	42.53
>7%	8,607	43.95	1,074	46.80
None	2,029	10.36	245	10.68
eGFR at baseline, n (%)				
≥60 mL/min/1.73 m^2	-	0.00	449	19.56
45-59 mL/min/1.73 m^2	14,851	75.84	1,134	49.41
30-44 mL/min/1.73 m^2	2,822	14.41	441	19.22
15-29 mL/min/1.73 m^2	1,062	5.42	179	7.80
<15 mL/min/1.73 m^2	847	4.33	65	2.83
None	-	0.00	27	1.18
Additional comorbidities				
Hypertension	14,994	76.57	1,906	83.05
Albuminuria	-	0.00	-	0.00
Primary hyperaldosteronism	26	0.13	15	0.65
Hyperkalemia	668	3.41	55	2.40
Congestive heart failure	1,755	8.96	645	28.10
Edema	775	3.96	229	9.98

RESULTS

Baseline characteristics

- A total of 80,348 patients had a diagnosis of diabetes and evidence of CKD. After application of the inclusion and exclusion criteria, a total of 19,582 patients were finally included in the analysis and 2,295 patients treated with MRA were included in the subcohort (Table 1).

Treatment patterns

- Percentages of users of renin-angiotensin-aldosterone system inhibitors at baseline were 52.3% in the overall cohort and 58.8% in the MRA subcohort (Figure 2).

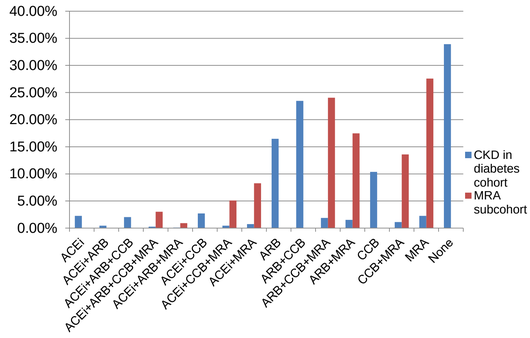

Figure 2. Treatment patterns of anti-hypertensive agents in CKD with diabetes at baseline

Crude event rates

- Table 2 shows crude event rates for hyperkalemia, renal, and CV-related events during the follow-up. Cumulative incidences of hyperkalemia were 5.19% in the overall cohort and 7.63% in the MRA subcohort. All event rates for renal and CV-related events were relatively higher among those in the MRA subcohort.

Table 2. Crude event rates for hyperkalemia, renal, and cardiovascular events

	CKD in diabetes cohort	MRA subcohort
At risk	*19,582*	*2,295*
Hyperkalemia		
N events	1,016	175
Event Rate (95% CI)	5.42 (5.09, 5.76)	8.06 (6.95, 9.35)
Renal failure		
N events	2,358	409
Event Rate (95% CI)	13.39 (12.86, 13.94)	20.64 (18.73, 22.74)
Reduction of eGFR ≥40%		
N events	1,643	466
Event Rate (95% CI)	8.86 (8.44, 9.3)	23.48 (21.44, 25.71)
Composite CV events*		
N events	4,536	840
Event Rate (95% CI)	28.77 (27.95, 29.62)	50.74 (47.43, 54.29)
Myocardial infarction		
N events	513	107
Event Rate (95% CI)	2.68 (2.46, 2.92)	4.85 (4.01, 5.86)
Stroke		
N events	2,963	343
Event Rate (95% CI)	17.48 (16.86, 18.12)	17.12 (15.4, 19.03)
Hospitalization for HF		
N events	1,515	537
Event Rate (95% CI)	8.17 (7.77, 8.59)	27.59 (25.35, 30.03)

Cox regression for hyperkalemia, renal, and CV-related events

- Table 3 and Table 4 demonstrate the hazard ratio (HR) of different eGFR levels at baseline for hyperkalemia, renal, and CV-related events in the entire cohort of CKD with diabetes and in the MRA subcohort.

Table 3. Cox regression for renal and cardiovascular events in the CKD in diabetes cohort

	eGFR level (mL/min/1.73 m^2)			
	45-59	30-44	15-29	<15
At risk	*14,851*	*2,822*	*1,062*	*847*
Hyperkalemia				
Event Rate (95% CI)	1.00 (ref)	3.50 (2.94, 4.15)	11.81 (10.03, 13.91)	12.17 (10.21, 14.51)
Renal failure				
Event Rate (95% CI)	1.00 (ref)	4.92 (4.40, 5.51)	18.90 (16.92, 21.10)	18.28 (16.23, 20.59)
Reduction of eGFR ≥40%				
Event Rate (95% CI)	1.00 (ref)	1.91 (1.31, 2.80)	4.31 (2.85, 6.52)	27.80 (20.69, 37.35)
Composite CV events*				
Event Rate (95% CI)	1.00 (ref)	1.22 (1.09, 1.36)	1.13 (0.95, 1.34)	1.00 (0.81, 1.23)
Myocardial infarction				
Event Rate (95% CI)	1.00 (ref)	1.09 (0.86, 1.39)	1.12 (0.78, 1.60)	1.31 (0.90, 1.91)
Stroke				
Event Rate (95% CI)	1.00 (ref)	1.12 (0.98, 1.28)	0.91 (0.73, 1.13)	0.88 (0.68, 1.14)
Hospitalization for HF				
Event Rate (95% CI)	1.00 (ref)	1.91 (1.68, 2.17)	3.13 (2.68, 3.66)	2.25 (1.84, 2.76)

Table 4. Cox regression for renal and cardiovascular events in the MRA subcohort

	eGFR level (mL/min/1.73 m^2)			
	45-59	30-44	15-29	<15
At risk	*1,134*	*441*	*179*	*65*
Hyperkalemia				
Event Rate (95% CI)	1.00 (ref)	1.84 (1.22, 2.77)	5.75 (3.85, 8.57)	6.37 (3.68, 11.00)
Renal failure				
Event Rate (95% CI)	1.00 (ref)	2.57 (1.52, 4.35)	7.36 (4.42, 12.26)	8.20 (4.24, 15.86)
Reduction of eGFR ≥40%				
Event Rate (95% CI)	1.00 (ref)	1.48 (1.16, 1.90)	2.47 (1.85, 3.29)	2.27 (1.43, 3.62)
Composite CV events*				
Event Rate (95% CI)	1.00 (ref)	0.92 (0.66, 1.28)	0.90 (0.56, 1.43)	0.84 (0.38, 1.84)
Myocardial infarction				
Event Rate (95% CI)	1.00 (ref)	0.17 (0.04, 0.68)	0.31 (0.06, 1.54)	0.38 (0.03, 4.97)
Stroke				
Event Rate (95% CI)	1.00 (ref)	1.06 (0.80, 1.40)	1.37 (0.96, 1.96)	0.96 (0.49, 1.87)
Hospitalization for HF				
Event Rate (95% CI)	1.00 (ref)	1.36 (1.09, 1.71)	2.55 (1.96, 3.30)	1.96 (1.26, 3.04)

LIMITATIONS

- The MDV database might not be a fully representative of diabetic patients with CKD in Japan
- Data on urinary albumin and biopsy were not available for the confirmation of the CKD diagnosis in diabetic patients
- Results from the subgroup analysis should be carefully interpreted due to the small sample size
- Some HRs in the Cox models may be difficult to interpret due to violation of the proportional-hazards assumption

CONCLUSIONS

There are residual risks for hyperkalemia, renal, and CV-related events in diabetic patients with CKD in real-world settings in Japan, even after treatment initiation with steroidal MRA drugs. The unmet needs and burden of disease should be considered in future treatment for CKD in diabetes.

* Composite CV events: the first event among myocardial infarction, stroke, or hospitalization for heart failure. All models were adjusted for age group (<50, 50-59, 60-69, and 70≥), gender, hypertension and hyperlipidemia at baseline. Abbreviations: ACEi, Angiotensin-Converting Enzyme inhibitor; ARB, Angiotensin II Receptor Blocker; CCB, Calcium Channel Blockers; CI, Confidence Interval; CV, Cardiovascular; CKD, Chronic Kidney Disease; DM, Diabetes Mellitus; HF, Heart Failure; HR, Hazard Ratio; MRA, Mineralocorticoid Receptor Antagonists.