Laboratory of Clinical Pharmacy[1], Gifu Pharmaceutical University, Gifu; Department of Pharmacy[2], Ichinomiya Municipal Hospital, Aichi; Department of Pharmacy[3], Laboratory of Community Health Pharmacy[4], Gifu Pharmaceutical University, Gifu, Japan

Relationship between initial renal function and the inhibitory effect of dipeptidyl peptidase-4 inhibitor treatment on renal function decline

H. Esaki[1,2], T. Tachi[1,3,*], C. Goto[3], Y. Noguchi[1], K. Tanaka[3], S. Aoyama[3], M. Yasuda[3], T. Mizui[3], M. Yamamura[2], H. Teramachi[1,4,*]

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**Corresponding authors: Tomoya Tachi, Laboratory of Clinical Pharmacy, Gifu Pharmaceutical University, 1-25-4, Daigakunishi, Gifu-shi, Gifu 501-1196, Japan*
tachi@gifu-pu.ac.jp
Hitomi Teramachi, Laboratory of Clinical Pharmacy, Gifu Pharmaceutical University, 1-25-4, Daigakunishi, Gifu-shi, Gifu 501-1196, Japan
teramachih@gifu-pu.ac.jp

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We retrospectively investigated the renal function index of patients with type 2 diabetes mellitus (T2DM) to examine the influence of dipeptidyl peptidase-4 (DPP-4) inhibitors on renal function between patients up to early nephropathy and after overt nephropathy. Patients with T2DM (>18 years old) who had been prescribed hypoglycemic agents for ≥3 months at Gifu Municipal Hospital between March 2010 and April 2014 were included in the study. Renal function was evaluated as the estimated glomerular filtration rate (eGFR) decline from baseline at 12 months. Patients in the DPP-4 inhibitor-treated and untreated groups with an eGFR ≥60 (358 [58.2 %] and 257 [41.8 %], respectively) and eGFR <60 (115 [60.2 %] and 76 [39.8 %], respectively) were subjected to multiple logistic regression analysis. Among patients with an eGFR ≥60, no significant differences were observed in eGFR decline rates over time. However, among patients with an eGFR <60, significant decreases were observed in eGFR decline rates >10 % (6 months; odds ratio, 0.476; P = 0.043, 12 months; odds ratio, 0.413; P = 0.010). Similar results were obtained for an eGFR decline rate >20 % (12 months; odds ratio, 0.369; P = 0.049). DPP-4 inhibitors are renoprotective in patients with T2DM and an eGFR <60.

1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors selectively inhibit the incretin-degrading enzyme DPP-4 to enhance the functions of endogenous incretins (Drucker and Nauck 2006). Incretins, which include glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide, are gut hormones secreted after food intake (Nauck et al. 2009). Incretins decrease blood glucose levels by promoting insulin secretion from pancreatic β-cells in a glucose concentration-dependent manner and by inhibiting glucagon secretion from α-cells (Holst et al. 2016; Idris and Donnelly 2007). According to recent reports, incretin receptors are present in various organs, and the effects of incretin are not limited to the pancreas (Kim and Samson 2014). The renoprotective effects of incretins are independent of their hypoglycemic effects and are likely mediated by the suppression of sodium reabsorption, as well as anti-oxidative and anti-inflammatory effects on the renal tubules (Fujita et al. 2014; Joo et al. 2013; Kodera et al. 2011; Mima et al. 2012; Vallon and Docherty 2014).

Diabetic nephropathy is one of three major complications of DM; this condition has been the primary cause of dialysis in Japan since 1998 and is currently the primary cause of end-stage renal disease (ESRD) in the United States. Degradation of renal function is a risk factor for ESRD, cardiovascular events, and death (Coresh et al. 2014; Hallan et al. 2012; Matsushita et al. 2010; So et al. 2006). In addition, ESRD requires dialysis treatments, which decrease the patient's quality of life (Feroze et al. 2011; Md Yusop et al. 2013; Saad et al. 2015). These data emphasize the need to prevent the development and progression of diabetic nephropathy and importance of delaying the degradation of renal function.

Recent investigations of the effects of DPP-4 inhibitors on renal function have revealed the renoprotective effects of these drugs (Chan et al. 2008; Esaki et al. 2017; Fujita et al. 2014; Groop et al. 2013; Groop et al. 2014; Kothny et al. 2012; McGill et al. 2013). Some previous studies of renin-angiotensin-aldosterone system inhibitors, which also have renoprotective effects, suggested that the patients' initial renal function level influenced the renoprotective effects of the inhibitors (Brenner et al. 2001; Hou et al. 2006; Hsu et al. 2014; Remuzzi et al. 2004; Ruggenenti et al. 2001). For example, the renoprotective agent

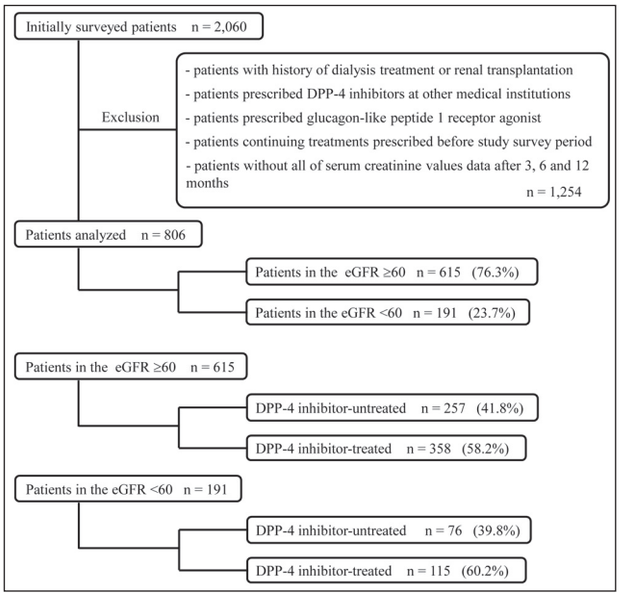

Fig. 1: Patient selection and breakdown

Table 1: Characteristics of patients

(A) Baseline eGFR ≥ 60

	Overall	DPP-4 inhibitors-untreated group	DPP-4 inhibitors-treated group	*P*-value
	(n = 615)	(n = 257)	(n = 358)	
Age (years)	62.1 ± 11.9	61.8 ± 12.6	62.3 ± 11.5	0.670
≥ 65 years [n (%)]	284 (46.2)	116 (45.1)	168 (46.9)	0.660
Male sex [n (%)]	410 (66.7)	170 (66.1)	240 (67.0)	0.817
Body height (cm)	161.6 ± 9.4	161.0 ± 9.2	162.0 ± 9.5	0.168
	(n = 577)	(n = 242)	(n = 335)	
Body weight (kg)	65.7 ± 15.5	65.7 ± 15.8	65.8 ± 15.3	0.950
	(n = 597)	(n = 252)	(n = 345)	
BMI (kg/m^2)	25.1 ± 4.9	25.3 ± 5.2	25.0 ± 4.7	0.541
	(n = 572)	(n = 242)	(n = 330)	
Systolic BP (mmHg)	134.9 ± 19.8	134.1 ± 19.4	135.5 ± 20.2	0.471
	(n = 442)	(n = 176)	(n = 266)	
Diastolic BP (mmHg)	78.7 ± 13.9	76.9 ± 13.4	79.9 ± 14.1	0.026*
	(n = 442)	(n = 176)	(n = 266)	
Laboratory findings				
Serum albumin (g/dL)	4.2 ± 0.5	4.2 ± 0.6	4.2 ± 0.5	0.371
	(n = 352)	(n = 155)	(n = 197)	
BUN (mg/dL)	14.3 ± 4.2	14.2 ± 4.3	14.4 ± 4.1	0.538
	(n = 606)	(n = 253)	(n = 353)	
Serum creatinine (mg/dL)	0.68 ± 0.15	0.69 ± 0.15	0.68 ± 0.14	0.423
	(n = 615)	(n = 257)	(n = 358)	
Uric acid (mg/dL)	5.3 ± 1.4	5.5 ± 1.4	5.3 ± 1.4	0.212
	(n = 250)	(n = 83)	(n = 167)	
Triglyceride (mg/dL)	164.1 ± 110.9	171.0 ± 120.8	159.9 ± 104.2	0.284
	(n = 490)	(n = 187)	(n = 303)	
HDL-cholesterol (mg/dL)	52.0 ± 15.1	52.9 ± 15.5	51.4 ± 14.9	0.298
	(n = 476)	(n = 177)	(n = 299)	
LDL-cholesterol (mg/dL)	112.9 ± 30.7	116.8 ± 32.1	110.8 ± 29.8	0.053
	(n = 437)	(n = 155)	(n = 282)	
Serum sodium (mEq/L)	139.2 ± 3.0	139.3 ± 3.1	139.2 ± 3.0	0.565
	(n = 470)	(n = 190)	(n = 280)	
Serum potassium (mEq/L)	4.2 ± 0.4	4.2 ± 0.5	4.3 ± 0.4	0.011*
	(n = 472)	(n = 192)	(n = 280)	
Serum chloride (mEq/L)	103.2 ± 3.4	103.3 ± 3.3	103.1 ± 3.4	0.576
	(n = 467)	(n = 189)	(n = 278)	
HbA1c (%)	8.1 ± 1.8	8.2 ± 2.0	8.1 ± 1.6	0.429
	(n = 582)	(n = 241)	(n = 341)	
eGFR (mL•min^{-1}•1.73 m$^{(2)-1}$)	86.4 ± 21.4	86.1 ± 23.6	86.6 ± 19.7	0.793
eGFR [n (%)]				
≥ 90 (mL•min^{-1}•1.73 m$^{(2)-1}$)	210 (34.1)	85 (33.1)	125 (34.9)	
60-90 (mL•min^{-1}•1.73 m$^{(2)-1}$)	405 (65.9)	172 (66.9)	233 (65.1)	
Relevant medical history				
Hypertension [n (%)]	334 (54.3)	137 (53.3)	197 (55.0)	0.673
Dyslipidemia [n (%)]	320 (52.0)	128 (49.8)	192 (53.6)	0.349
Hyperuricemia [n (%)]	48 (7.8)	23 (8.9)	25 (7.0)	0.370

(B) Baseline eGFR < 60

	Overall	DPP-4 inhibitors-untreated group	DPP-4 inhibitors-treated group	*P*-value
	(n = 191)	(n = 76)	(n = 115)	
Age (years)	72.0 ± 9.2	71.9 ± 8.8	72.0 ± 9.6	0.946
≥ 65 years [n (%)]	151 (79.1)	63 (82.9)	88 (76.5)	0.289
Male sex [n (%)]	109 (57.1)	48 (63.2)	61 (53.0)	0.167
Body height (cm)	158.3 ± 9.2	159.2 ± 9.8	157.6 ± 8.7	0.247
	(n = 184)	(n = 74)	(n = 110)	
Body weight (kg)	61.7 ± 12.2	62.7 ± 13.0	61.0 ± 11.5	0.330
	(n = 183)	(n = 74)	(n = 109)	
BMI (kg/m^2)	24.4 ± 3.9	24.5 ± 4.0	24.4 ± 3.9	0.937
	(n = 179)	(n = 73)	(n = 106)	
Systolic BP (mmHg)	134.3 ± 22.7	125.6 ± 17.0	139.5 ± 24.1	< 0.001*
	(n = 139)	(n = 52)	(n = 87)	
Diastolic BP (mmHg)	73.0 ± 14.1	68.9 ± 12.1	75.4 ± 14.7	0.008*
	(n = 139)	(n = 52)	(n = 87)	
Laboratory findings				
Serum albumin (g/dL)	4.0 ± 0.6	3.9 ± 0.7	4.1 ± 0.6	0.038*
	(n = 127)	(n = 54)	(n = 73)	
BUN (mg/dL)	23.2 ± 10.7	25.5 ± 13.1	21.7 ± 8.4	0.026*
	(n = 190)	(n = 76)	(n = 114)	
Serum creatinine (mg/dL)	1.24 ± 0.55	1.38 ± 0.73	1.14 ± 0.37	0.008*
	(n = 191)	(n = 76)	(n = 115)	
Uric acid (mg/dL)	6.1 ± 1.6	6.1 ± 1.8	6.1 ± 1.5	0.819
	(n = 87)	(n = 33)	(n = 54)	
Triglyceride (mg/dL)	178.8 ± 150.6	188.7 ± 185.2	173.3 ± 128.7	0.574
	(n = 133)	(n = 47)	(n = 86)	
HDL-cholesterol (mg/dL)	49.4 ± 14.2	49.0 ± 16.3	49.6 ± 13.0	0.809
	(n = 128)	(n = 44)	(n = 84)	
LDL-cholesterol (mg/dL)	108.1 ± 28.9	108.1 ± 32.6	108.1 ± 27.1	0.990
	(n = 121)	(n = 40)	(n = 81)	
Serum sodium (mEq/L)	139.0 ± 3.0	138.5 ± 3.5	139.3 ± 2.7	0.085
	(n = 163)	(n = 60)	(n = 103)	
Serum potassium (mEq/L)	4.5 ± 0.5	4.5 ± 0.5	4.4 ± 0.5	0.240
	(n = 163)	(n = 60)	(n = 103)	
Serum chloride (mEq/L)	103.9 ± 3.5	104.2 ± 4.2	103.8 ± 3.1	0.537
	(n = 161)	(n = 58)	(n = 103)	
HbA1c (%)	7.8 ± 1.7	7.7 ± 2.2	7.8 ± 1.2	0.505
	(n = 176)	(n = 67)	(n = 109)	
eGFR (mL•min^{-1}•1.73 m$^{(2)-1}$)	45.2 ± 12.8	43.0 ± 14.4	46.7 ± 11.4	0.056
eGFR [n (%)]				
45-60 (mL•min^{-1}•1.73 m$^{(2)-1}$)	127 (66.5)	49 (64.5)	78 (67.8)	
30-45 (mL•min^{-1}•1.73 m$^{(2)-1}$)	44 (23.0)	13 (17.1)	31 (27.0)	
15-30 (mL•min^{-1}•1.73 m$^{(2)-1}$)	31 (16.2)	17 (22.4)	14 (12.2)	
< 15 (mL•min^{-1}•1.73 m$^{(2)-1}$)	3 (1.6)	3 (3.9)	0 (0.0)	
Relevant medical history				
Hypertension [n (%)]	156 (81.7)	62 (81.6)	94 (81.7)	0.978
Dyslipidemia [n (%)]	116 (60.7)	37 (48.7)	79 (68.7)	0.006*
Hyperuricemia [n (%)]	35 (18.3)	15 (19.7)	20 (17.4)	0.682

Data are expressed as means±standard deviations unless otherwise indicated.
Abbreviations: DPP-4, dipeptidyl peptidase-4; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate. *$P < 0.05$.

Table 2: Medication use

(A) Patients with a baseline eGFR ≥60

	DPP-4 inhibitors-untreated group (n = 257)		DPP-4 inhibitors-treated group (n = 358)		*P*-value
Hypoglycemic agents					
DPP-4 inhibitors					
Sitagliptin [n (%)]			229	(64.0)	
Vildagliptin [n (%)]			92	(25.7)	
Alogliptin [n (%)]			25	(7.0)	
Linagliptin [n (%)]			8	(2.2)	
Teneligliptin [n (%)]			4	(1.1)	
Biguanides [n (%)]	114	(44.4)	114	(31.8)	0.002*
α-Glucosidase inhibitors [n (%)]	108	(42.0)	80	(22.3)	< 0.001*
Insulin [n (%)]	86	(33.5)	59	(16.5)	< 0.001*
Sulfonylureas [n (%)]	56	(21.8)	88	(24.6)	0.441
Thiazolidines [n (%)]	40	(15.6)	38	(10.6)	0.085
Glinides [n (%)]	23	(8.9)	3	(0.8)	< 0.001*
Other combination drug					
ACEI/ARBs [n (%)]	84	(32.7)	98	(27.4)	
Statins [n (%)]	76	(29.6)	116	(32.4)	
Nephrotoxic agents [n (%)]	141	(54.9)	184	(51.4)	

(B) Patients with a baseline eGFR <60

	DPP-4 inhibitors-untreated group (n = 76)		DPP-4 inhibitors-treated group (n = 115)		*P*-value
Hypoglycemic agents					
DPP-4 inhibitors					
Sitagliptin [n (%)]			61	(53.0)	
Vildagliptin [n (%)]			33	(28.7)	
Alogliptin [n (%)]			9	(7.8)	
Linagliptin [n (%)]			8	(7.0)	
Teneligliptin [n (%)]			4	(3.5)	
Biguanides [n (%)]	13	(17.1)	28	(24.3)	0.281
α-Glucosidase inhibitors [n (%)]	38	(50.0)	28	(24.3)	< 0.001*
Insulin [n (%)]	26	(34.2)	23	(20.0)	0.042*
Sulfonylureas [n (%)]	19	(25.0)	27	(23.5)	0.863
Thiazolidines [n (%)]	16	(21.1)	14	(12.2)	0.108
Glinides [n (%)]	11	(14.5)	0	(0.0)	< 0.001*
Other combination drug					
ACEI/ARBs [n (%)]	29	(38.2)	60	(52.2)	
Statins [n (%)]	20	(26.3)	41	(35.7)	
Nephrotoxic agents [n (%)]	47	(61.8)	81	(70.4)	

Abbreviations: DPP-4, dipeptidyl peptidase-4; ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers. *$P < 0.05$.

losartan was shown to reduce the incidence of ESRD more remarkably among patients with a lower initial estimated glomerular filtration rate (eGFR) (Brenner et al. 2001; Remuzzi et al. 2004). However, no reports have addressed the influence of the patient's initial renal function on the renoprotective effects of DPP-4 inhibitors.

In this study, we stratified patients with T2DM who were treated with hypoglycemic agents into two groups corresponding to up to early nephropathy and overt nephropathy and beyond, and conducted a retrospective analysis to clarify the interaction of initial renal function and DPP-4 inhibitor monotherapy on subsequent renal function in both groups. We used multiple classification methods to avoid confounding biases while assessing the renoprotective effects of DPP-4 inhibitors.

2. Investigations and results

2.1. Patient selection

Of the 2,060 patients initially surveyed for study inclusion, 806 were included in the multiple logistic regression analysis and

stratified into eGFR ≥60 (615 patients, 76.3 %) and eGFR <60 groups (191, 23.7 %) (Fig. 1). Patients in both groups were further categorized into eGFR ≥60 DPP-4 inhibitor-untreated and treated groups (eGFR ≥60: 257, 41.8 % and 358, 58.2 %, respectively; eGFR <60: 76, 39.8 % and 115, 60.2 %, respectively) (Fig. 2).

2.2. Patients' baseline characteristics

The baseline characteristics of patients in the eGFR ≥60 group are shown in Table 1A. The average (±standard deviation) age was 62.1±11.9 years, and 46.2 % of the patients were older than 65 years (66.7 % men). Hypertension, dyslipidemia, and hyperuri-

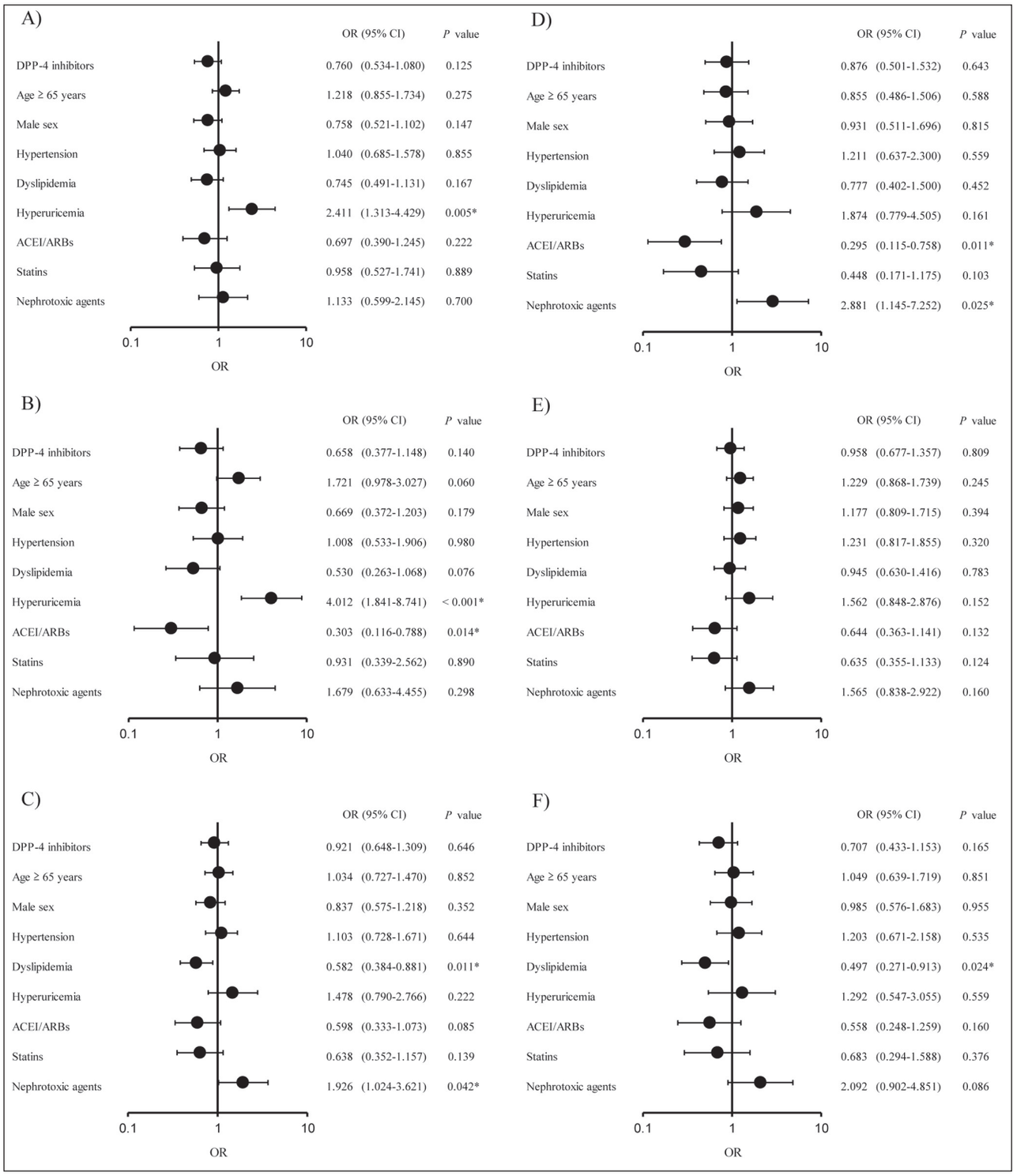

Fig. 2: Multiple logistic regression analysis of patients with an eGFR ≥60, A) eGFR decline >10 % after 3 months, B) eGFR decline >10 % after 6 months, C) eGFR decline >10 % after 12 months, D) eGFR decline >20 % after 3 months, E) eGFR decline >20 % after 6 months, F) eGFR decline >20 % after 12 months
Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; HR, hazard ratio. *$P < 0.05$

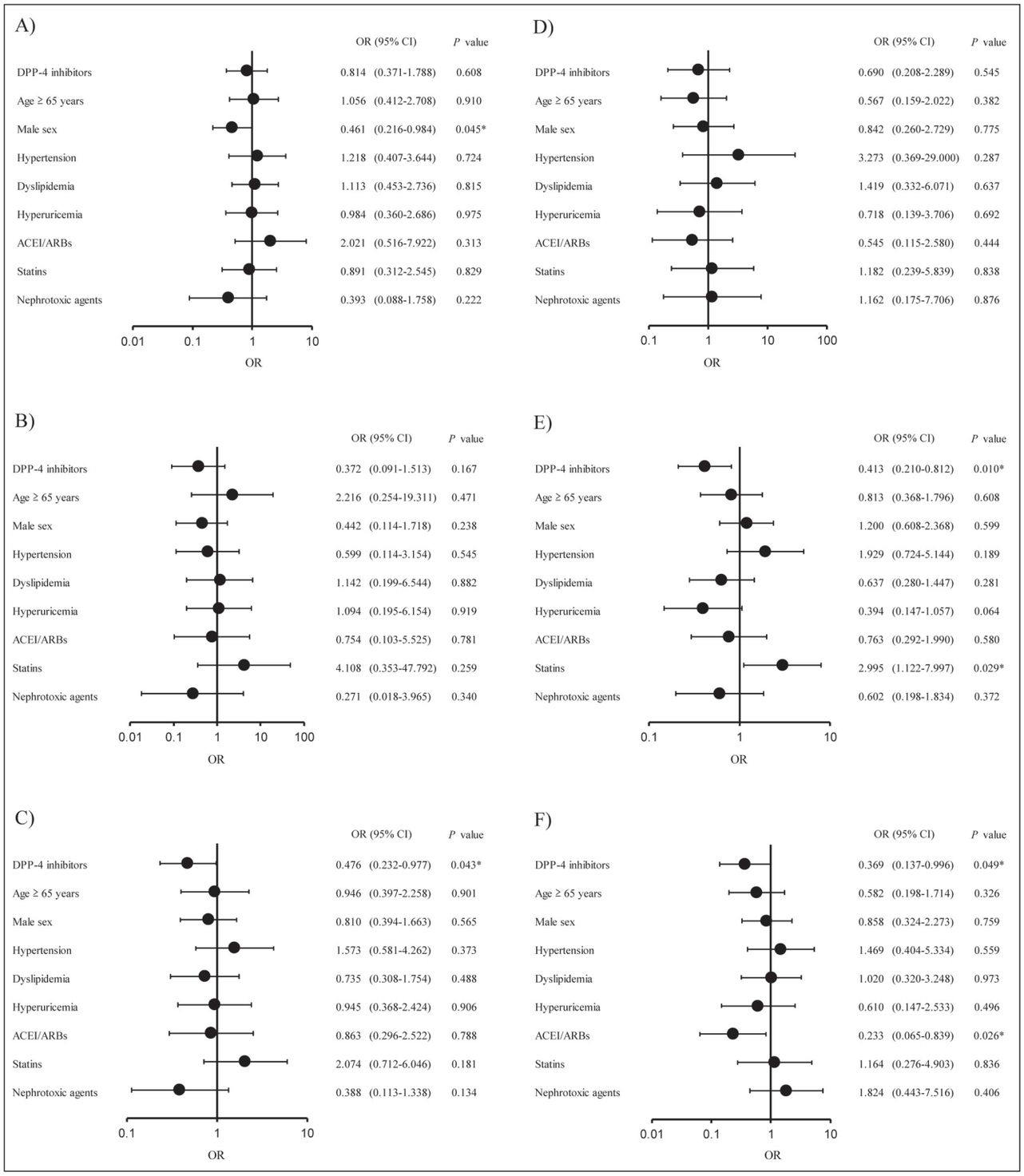

Fig. 3: Multiple logistic regression analysis of patients with an eGFR <60. **A)** eGFR decline >10 % after 3 months, **B)** eGFR decline >10 % after 6 months, **C)** eGFR decline >10 % after 12 months, **D)** eGFR decline >20 % after 3 months, **E)** eGFR decline >20 % after 6 months, **F)** eGFR decline >20 % after 12 months
Abbreviations: eGFR, estimated glomerular filtration rate; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; OR, odds ratio. *$P < 0.05$

cemia were reported in 54.3 %, 52.0 %, and 7.8 % of the patients, respectively. Patients treated with DPP-4 inhibitors had a significantly higher diastolic blood pressure [BP] and serum potassium level, compared to untreated patients.

The baseline characteristics of patients in the eGFR <60 group are shown in Table 1B. The average patient age was 72.0±9.2 years, and 79.1 % of the patients were older than 65 years (57.1 % men). Hypertension, dyslipidemia, and hyperuricemia were reported for 81.7 %, 60.7 %, and 18.3 % of the patients. In this group, patients treated with DPP-4 inhibitors had a significantly higher systolic BP, diastolic BP, serum albumin level, and incidence of dyslipidemia, as well as a significantly lower low density lipoprotein (LDL) cholesterol level, relative to untreated patients.

Differences in hemoglobin A1c (HbA1c) levels or eGFR were not observed in either group.

2.3. Concurrent medication use by patients

The medications concurrently used by patients with an eGFR ³60 are shown in Table 2A. Patients not treated with DPP-4 inhibitors were most commonly prescribed biguanides (114 patients, 44.4 %). The most commonly prescribed DPP-4 inhibitors were sitagliptin (229 patients, 64.0 %), vildagliptin (92, 25.7 %), alogliptin (25, 7.0 %), linagliptin (8, 2.2 %), and teneligliptin (4, 1.1 %). Biguanides were the most commonly prescribed among other hypoglycemic agents (114, 31.8 %).

An analysis of the medications concurrently used by patients with an eGFR <60 is shown in Table 2B. Patients not treated with DPP-4 inhibitors were most commonly treated with α-glucosidase inhibitors (38, 50.0 %). Patients were prescribed the following DPP-4 inhibitors: sitagliptin (61, 53.0 %), vildagliptin (33, 28.7 %), alogliptin (9, 7.8 %), linagliptin (8, 7.0 %), and teneligliptin (4, 3.5 %), whereas biguanides (28, 24.3 %) and α-glucosidase inhibitors (28, 24.3 %) were the most commonly prescribed among other hypoglycemic agents.

2.4. Patients with up to early nephropathy

The results of a multiple logistic regression analysis of patients with up to early nephropathy (i.e., eGFR ≥60) are shown in Fig. 2. No significant difference was observed in the effects of DPP-4 inhibitors on eGFR declines of >10 % during each period (Fig. 2A–C). The risk of an eGFR decline >10 % was significantly increased by hyperuricemia for 3 months (odds ratio [OR], 2.411; 95 % confidence interval [CI], 1.313-4.429; $P = 0.005$) (Fig. 2A) and nephrotoxic agents over 6 months (OR, 1.926; 95 % CI, 1.024-3.621; $P = 0.042$) (Fig. 2B).

Correspondingly, no significant difference was observed in the effects of DPP-4 inhibitors on the risk of an eGFR decline >20 % during each period (Fig. 2A–3C). Angiotensin-converting enzyme inhibitors (ACEI)/ARB use significantly reduced the risks of an eGFR decline >20 % over 3 months (OR, 0.303; 95 % CI, 0.116-0.788; $P = 0.014$) (Fig. 2D) and 6 months (OR, 0.295; 95 % CI, 0.115-0.758; $P = 0.025$) (Fig. 2E), as did the occurrence of dyslipidemia over 12 months (OR, 0.497; 95 % CI, 0.271-0.913; $P = 0.024$) (Fig. 2F). However, hyperuricemia over a period of 3 months (OR, 4.012; 95 % CI, 1.841-8.741; $P < 0.001$) and the use of nephrotoxic agents over 6 months (OR, 2.881; 95 % CI, 1.145-7.252; $P = 0.025$) increased the risk of an eGFR decline >20 % (Fig. 2D, 3E).

2.5. Patients with overt nephropathy or beyond

The results of a multiple logistic regression analysis of patients with overt nephropathy or beyond (i.e., eGFR <60) are shown in Fig. 3. In this group, DPP-4 inhibitor use significantly reduced the risk of an eGFR decline >10 % over 6 months (OR, 0.476; 95 % CI, 0.232-0.977; $P = 0.043$) and 12 months (OR, 0.413; 95 % CI, 0.210-0.812; $P = 0.010$) (Fig. 3B, C). Additionally, male sex significantly reduced the risk of an eGFR decline >10 % over 3 months (OR, 0.461; 95 % CI, 0.216-0.984; $P = 0.045$) (Fig. 3A), whereas statin use increased the risk over 12 months (OR, 2.995; 95 % CI, 1.122-7.997; $P = 0.029$) (Fig. 3C).

Among these patients, no significant sub-group difference was observed when analyzing eGFR declines of >20 % over 3 and 6 months (Fig. 3D, E); however, DPP-4 inhibitor use (OR, 0.369; 95 % CI, 0.137-0.996; $P = 0.049$) and ACEI/ARB use (OR, 0.233; 95 % CI, 0.065-0.839; $P = 0.026$) significantly reduced the risk of an eGFR decline >20 % over 12 months (Fig. 3F).

3. Discussion

This study used a multivariate analysis to examine the effects of DPP-4 inhibitors on renal function and the relationship with baseline renal function in patients with type 2 DM. Notably, no significant differences in eGFR decline rates of >10 % and >20 % were observed among patients with an eGFR ≥60 in any period, regardless of DPP-4 inhibitor use. These findings suggest that DPP-4 inhibitors did not inhibit renal function declines in patients with up to early nephropathy. By contrast, among patients with an eGFR <60, the ORs of an eGFR decline >10 % after 6 months and >20 % after 6 and 12 months were significantly lower among patients treated with DPP-4 inhibitors, suggesting that these drugs suppressed further renal function deterioration. In other words, DPP-4 inhibitors appeared to be renoprotective, particularly in patients with a low baseline level of kidney function.

Although DPP-4 inhibitor use significantly reduced the risk of an eGFR decline of >10 % at 6 and 12 months in patients with a low baseline eGFR, a significant reduction in the risk of an eGFR decline >20 % was only observed after 12 months. This difference might be attributable to the large number of qualifying patients who experienced eGFR declines >10 %, whereas fewer patients experienced an eGFR decline >20 % after 6 months. Accordingly, the multiple logistic regression analysis might not have distinguished a significant difference in the latter metric.

Previous reports suggested that strict blood glucose control suppresses the onset and progression of diabetic nephropathy in patients with diabetes (Duckworth et al. 2009; Group et al. 2008, 2011; Group 1998; Ismail-Beigi et al. 2010), thus underscoring the importance of glycemic control via hypoglycemic agents. However, many hypoglycemic drugs warrant attention in the context of decreased renal function. A previous report suggested a reduction in HbA1c with a low risk of hypoglycemia following the single administration of a DPP-4 inhibitor (Idris and Donnelly 2007). Moreover, contraindications for DPP-4 inhibitor use have not been reported. Furthermore, the dosages of these drugs can be adjusted when renal function decreases, and linagliptin, vildagliptin, and teneligliptin contribute significantly to liver metabolism and can be administered without dosage adjustments to patients with decreased renal function. Based on the results of this study, DPP-4 inhibitors exert a renoprotective effect, especially in patients with a baseline eGFR <60. Therefore, these drugs can be administered to patients with type 2 DM and poor renal function, in whom both the renoprotective and hypoglycemic effects are considered useful for blood glucose control.

This study only investigated patients for whom serum creatinine levels were available, which allowed the use of the eGFR reduction rate as an outcome variable. However, fewer patients had simultaneously available HbA1c data, and we did not incorporate this parameter as an independent variable. Still, to investigate changes in blood glucose levels between groups, we compared the rates of HbA1c decline after 12 months in 745 patients for whom both HbA1c and serum creatinine data were available. Notably, we observed no significant differences between DPP-4 inhibitor-untreated and treated patients in the eGFR ≥60 (10.4 % vs. 9.9 %, $P = 0.716$) or eGFR <60 group (8.6 % vs. 6.5 %, $P = 0.351$). Although we note that different numbers of patients were analyzed in the two groups, we observed no difference in the rate of HbA1c decline. However, the observation of improved renal function in the DPP-4 inhibitor-treated group suggests that these drugs exert their renoprotective effects independently of their antihyperglycemic effects.

Regarding additional limitations, we further note that in this study, the breakdown of the prescribed DPP-4 inhibitors was biased. Therefore, we did not compare the renoprotective effects of individual agents. However, these inhibitors may differ in terms of renoprotective effects, and these effects may depend on differences in drug profiles. Thus, a comparison of the effects of individual agents is needed. Moreover, both a reduced eGFR and albuminuria have been reported as predictors of renal outcomes in DM patients (Monseu et al. 2015; Tanaka et al. 2015), and the presence of microalbuminuria is considered important to the diagnosis of diabetic nephropathy. However, we did not analyze albuminuria in this study because of the insufficient availability of data.

Taken together, the findings of this study suggest that DPP-4 inhibitors suppress eGFR decreases in patients with T2DM and baseline eGFR <60; in other words, these drugs have renoprotective effects. Both the hypoglycemic effects and renoprotective effects of DPP-4 inhibitors, as clarified in this study, indicate that these drugs are useful for the treatment of patients with type 2 DM and poor kidney function. However, further prospective studies are necessary.

4. Experimental

4.1. Patients

Patients with T2DM (>18 years old) who had been prescribed hypoglycemic agents for ≥3 months at Gifu Municipal Hospital between March 2010 and April 2014 were retrospectively considered for inclusion in this study.

Patient data (age, sex, body height, body weight, systolic BP, diastolic BP, laboratory data, relevant medical history, and concurrent medications) from electronic health records were analyzed. The patient laboratory data included serum albumin, blood urea nitrogen, serum creatinine, uric acid, neutral fat, high density lipoprotein (HDL) cholesterol, LDL cholesterol, serum sodium, serum potassium, serum chloride, and HbA1c levels at baseline and after 3, 6, and 12 months. We also collected medical history records of hypertension, dyslipidemia, hyperuricemia, diseases affecting renal function, and the duration of treatment with hypoglycemic or potentially nephrotoxic agents (Perazella 2009). Patients with a history of dialysis treatment or renal transplantation, those prescribed DPP-4 inhibitors at other medical institutions, those prescribed glucagon-like peptide 1 receptor agonists, and those continuing treatment with hypoglycemic agents prescribed before the survey period for this study were excluded.

Patients with available serum creatinine data at baseline and after 3, 6, or 12 months were included in the multiple logistic regression analysis. We used these data to assess renal function by determining the eGFR decline. The eGFR was calculated using the following formula: $eGFR = 194 \times \text{serum creatinine}^{-1.094} \times age^{-0.287}$ ($mL \bullet min^{-1} \bullet 1.73\ m^{(2)-1}$), and was adjusted to eGFR × 0.739 for female patients. We defined an eGFR decline after 3 months as $(eGFR_{baseline} - eGFR_{3\ months})/\ eGFR_{baseline} \times 100$. Declines in eGFR after 6 and 12 months were defined analogously.

4.2. Statistical analysis

We used IBM SPSS statistics software, version 24.0J (Armonk, NY, USA) for the statistical analysis. To examine the influence of DPP-4 inhibitors on renal function between patients up to early nephropathy and those with overt nephropathy and beyond, we stratified patients into two groups: eGFR ≥60 and eGFR <60. The unpaired *t* test and χ^2 test were used to analyze differences between DPP-4 inhibitor-treated and untreated patients in both groups. A multiple logistic regression analysis was performed using an eGFR decline of >10 % or >20 % as the dependent variable and "DPP-4 inhibitors", "age ≥65 years" (Kazancioglu 2013; Yamagata et al. 2007), "male sex" (Hauteclocque et al. 2014; Kazancioglu 2013), "hypertension" (Higashikuni et al. 2008; Rossing et al. 2004), "dyslipidemia" (Muntner et al. 2000; Schaeffner et al. 2003; Yamagata et al. 2007), "hyperuricemia" (Li et al. 2014; Yamagata et al. 2007), "ACEI/angiotensin II receptor blockers (ARBs)" (Brenner et al. 2001; Lee et al. 2002; Lewis et al. 1993; Ruggenenti et al. 2010), "statins" (Lee et al. 2002; Tonelli et al. 2005), and "nephrotoxic agents" (Perazella 2009) as independent variables to avoid confounding biases. *P* values <0.05 were considered statistically significant.

4.3. Ethical considerations

This study was approved by the Ethical Review Board of Gifu Municipal Hospital (approval number: 203) and the Bioethics Committee of Gifu Pharmaceutical University (approval number: Hei27-14). Furthermore, this study used an opt-out consent approach that was approved by both ethical committees in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects, announced by the Ministry of Health, Labor, and Welfare in Japan.

Author Contributions: All authors contributed to the study design. All authors participated in collecting and interpreting the data. HE analyzed data and drafted the manuscript. TT confirmed the analyzed data and revised the manuscript. All authors reviewed and approved the final manuscript.

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