

# Nonadherence of Oral Antihyperglycemic Medication Will Increase Risk of End-Stage Renal Disease

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**Abstract:** Poor glycemic control is related to an increased risk of end-stage renal disease (ESRD). This study investigated the association between medication adherence and the risk of ESRD in patients with newly diagnosed diabetes mellitus.

In this population-based cohort study, we used the Taiwan National Health Insurance Research Database (NHIRD) to identify 559,864 patients with newly diagnosed or treated diabetes mellitus who were ages from 20 to 85 years between 2001 and 2008. We identified 1695 patients with ESRD during the study period. The mean follow-up time of the patients with ESRD was 5.7 years. Time-dependent Cox proportional hazards regression was performed to estimate the hazard ratios for ESRD among the patients with newly diagnosed diabetes mellitus.

After adjustment for various covariates, nonadherence to oral antihyperglycemic medication (OAM) was associated with a higher risk of ESRD compared with adherence to OAM (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.01–1.23). The effects of nonadherence to OAM on the risk of ESRD were significant for patients without hypertension, without gout, without chronic kidney disease, undergoing OAM polytherapy, and undergoing metformin polytherapy (HR [95% CIs], 1.18 [1.00–1.39], 1.13 [1.02–1.26], 1.17 [1.03–1.33], 1.22 [1.08–1.38], and 1.13 [1.02–1.25], respectively).

In conclusion, nonadherence to OAM therapy is associated with ESRD. Adherence to medication therapy can prevent the progressive loss of renal function and ESRD for patients with diabetes.

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**Abbreviations:** CCI = Charlson comorbidity index, CI = confidence interval, CKD = chronic kidney disease, CVD = cardiovascular disease, ESRD = end-stage renal disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, MPR = medication possession ratio, NHIRD = National Health Insurance Research Database, NSAIDs = nonsteroidal anti-inflammatory drugs, OAM = oral antihyperglycemic medication.

## INTRODUCTION

The prevalence of end-stage renal disease (ESRD) is approaching an unprecedented level. According to the 2013 US Renal Data System Annual Data Report, 430,273 of the 615,899 patients receiving ESRD therapy also received dialysis treatment at the end of 2011.<sup>1</sup> Patients with ESRD receiving dialysis are at a considerably increased risk of myocardial infarction, ischemic stroke, cardiovascular disease (CVD), and all-cause mortality compared with the general population.<sup>2–4</sup> Furthermore, diabetes mellitus, hypertension, hyperlipidemia, and CVD are regarded as risk factors of ESRD.<sup>5,6</sup> Among these risk factors, diabetes has been strongly associated with ESRD. An investigation in 2011 indicated that 44% of patients with newly diagnosed ESRD (157 million) have diabetes, whereas only 28% (101 million) of those cases were due to hypertension.<sup>1</sup> Another previous study showed that 29% to 47% of people with type 2 diabetes developed chronic kidney disease (CKD).<sup>7</sup> Patients with diabetes gradually develop glomerular and renal hypertrophy, lead to increased urinary albumin and pathologic alterations of the tubulointerstitium, such as fibrosis and tubular atrophy. This causes a decline in the glomerular filtration rate over years or decades, eventually leading to ESRD.<sup>8</sup>

Previous studies have proposed prescribing intensive glucose-lowering regimens to prevent the development of ESRD<sup>9</sup> and reduce the risk of microalbuminuria and macroalbuminuria.<sup>10–12</sup> For patients with diabetes, medication adherence is critical in managing their condition.<sup>13</sup> The medication adherence rate of patients with diabetes range from 36% to 93%,<sup>14</sup> and lower adherence or poorer glycemic control might result in a higher risk of complications and disability, as well as higher healthcare costs and mortality.<sup>15–17</sup>

A previous study have indicated that the risk of ESRD can be reduced by improving antihypertensive medication adherence.<sup>18</sup> Furthermore, other studies have argued that improved antihyperglycemic medication adherence or strict glycemic control can effectively prevent CVD, improve cerebrovascular outcomes, and delay the onset of diabetes complications.<sup>15,19–21</sup> However, to our knowledge, no study has assessed the association between antihyperglycemic medication adherence and subsequent development of ESRD. Therefore, this study investigated the association between antihyperglycemic medication adherence and the risk of ESRD among patients with newly diagnosed type 2 diabetes.

## METHODS

### Dataset Source

In this population-based cohort study, we used the data from Taiwan National Health Insurance Research Database (NHIRD), which contains the healthcare data of more than 95% of the hospitals in Taiwan and 99% of the approximately 23 million NHI program enrollees.<sup>22,23</sup> The NHIRD includes inpatient, outpatient, and prescription information containing final action paid claims submitted by healthcare providers. The data include information on disease diagnoses coded in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) treatment procedures, drug prescriptions, reimbursements, amounts, beneficiary's encrypted demographic information (e.g., service dates, birth dates, sex, residency area) and provider's information.<sup>22,24</sup> In this study, we obtained data from the NHIRD for the period of 2000 to 2010. Because NHIRD dataset is encrypted secondary data, it is impossible to identify individual person. Approved was received from the Taipei Medical University Joint Institutional Review Board (Approval No. 201204036).

### Design and Study Participants

We identified data on patients ages between 20 and 85 years with diagnosed type 2 diabetes (ICD-9-CM Codes 250.xx; excluding type 1 diabetes, Codes 250.x1 and 250.x3) and treated with either biguanides, sulfonamides, urea derivatives,  $\alpha$ -glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4, or a combination of oral antihyperglycemic agents between January 1, 2001 and December 31, 2008. We limited the included patients to those who had more than 3 physician visits separated at intervals exceeding 28 days in any year in the study period, in accordance with the American Diabetes Association Clinical Practice Recommendations.<sup>25</sup> Among those patients, we regarded their first clinical visit where antihyperglycemic medication was prescribed to treat diabetes as the onset of diabetes and index date for this study. Additionally, we used a 2-year washout period to ensure that all cases of diabetes were incident. Therefore, patients who had any diagnostic claims of diabetes or had any antihyperglycemic agent in 1999 and 2000 were excluded, resulting in a research sample comprising 1,239,635 patients.

Furthermore, patients were excluded from the analysis if they met any of the following criteria: a history of dialysis treatment before the index date; a history of autoimmune disease or cancer, because these conditions are highly associated with kidney disease and are strong predictors of ESRD; had been prescribed insulin during any year in the study period, because the claims data did not provide sufficient information regarding the insulin regimen of each patient, such as the use of a sliding-scale insulin regimen<sup>26,27</sup>; and had been prescribed any antihyperglycemic medication <12 months before undergoing dialysis treatment, because we could not determine whether ESRD was related to pharmacological therapy. Patients who had ESRD within 2 years of follow-up were also excluded because it was difficult to ensure whether the outcomes could be attributed to their antihyperglycemic medication adherence.

The final cohort comprised 559,864 patients who were followed from the 3rd year after the index date until ESRD onset, death, or the end of the study period (December 31, 2010). Patients with no predefined outcome or died during follow-up were censored. The patients were followed for a minimum of 12 months to a maximum of 7 years.

### Medication Adherence During Follow-Up

Adherence to antihyperglycemic treatment was defined as the consumption of oral antihyperglycemic medication (OAM) as prescribed, and this was estimated using the medication possession ratio (MPR), which was calculated by taking the total number of days for which medication was prescribed and dividing it by the number of days in a year (365). Patients with an MPR lower than the cutoff point of 80% were regarded as nonadherent.<sup>18,27,28</sup> In this study, we measured the patient's adherence started from the 3rd year of the index date of diabetes to ESRD onset or the end of the study period (December 31, 2010). We did not measure the adherence in the first 2 years because patients with newly diagnosed diabetes could deny receiving the treatment of medications; this might produce misleading results regarding the effect of treatment adherence.<sup>29</sup>

### Main Outcome Measurements and Covariate Assessment

The outcome was ESRD, which was defined as the continual receipt of dialysis treatment for 3 months according to the claims data. Several covariates, namely age, sex, comorbidities, and medication use, were considered. Hypertension was defined according to ICD-9-CM Codes 401 to 405 and whether antihypertensive medications were prescribed. The comorbidities considered in this study were gout (ICD-9-CM Code 274), ischemic heart disease (ICD-9-CM Codes 410–414), cerebrovascular disease (ICD-9-CM Codes 430–438), peripheral arterial disease (ICD-9-CM Codes 440–444, 447, and 557), congestive heart failure (ICD-9-CM Codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7, 425.8, 425.9, and 428), anemia (ICD-9-CM Codes 280–289), and CKD (ICD-9-CM Codes 016.0, 095.4, 189, 223, 236.9, 250.4, 271.4, 274.1, 283.11, 403–404, 440.1, 442.1, 447.3, 572.4, 581–584, 586–588, 591, 642.1, 646.2, 753, and 794.4).

The Charlson comorbidity index (CCI), which is a scoring system for weighting factors on critical concomitant diseases defined by the ICD-9-CM,<sup>30</sup> was used in this study. We also considered the effect of the type of pharmacotherapy. To measure of the severity of diabetes, OAM was classified according to the type (metformin and nonmetformin) and number (monotherapy and polytherapy) of prescribed medications. For medications other than OAM, we considered prescriptions of nonsteroidal anti-inflammatory drugs (NSAIDs) and statins. In addition, patients with both diabetes and hypertension who had poor medication adherence for hypertension were associated with an increased risk of ESRD. Therefore, we indirectly measured the severity of hypertension according to the number of prescribed antihypertensive agents (monotherapy and polytherapy).

We determined whether the interactive effects of the CCI and medication adherence affected the patients' ESRD risk before the onset of their diabetes by performing an additional analysis. A model was created to evaluate the effects of CCI and adherence on ESRD risk by stratifying the patients into the following 4 groups: patients who adhered to OAM with a CCI  $\leq 1$  (reference group); patients who adhered to OAM with a CCI  $\geq 2$ ; patients who were nonadherent to OAM with a CCI  $\leq 1$ ; and patients who were nonadherent to OAM with a CCI  $\geq 2$ . In these models, all baseline characteristics were adjusted.

All covariates were defined according to the presence of ICD-9-CM or medical procedures in the first 2 years of onset.

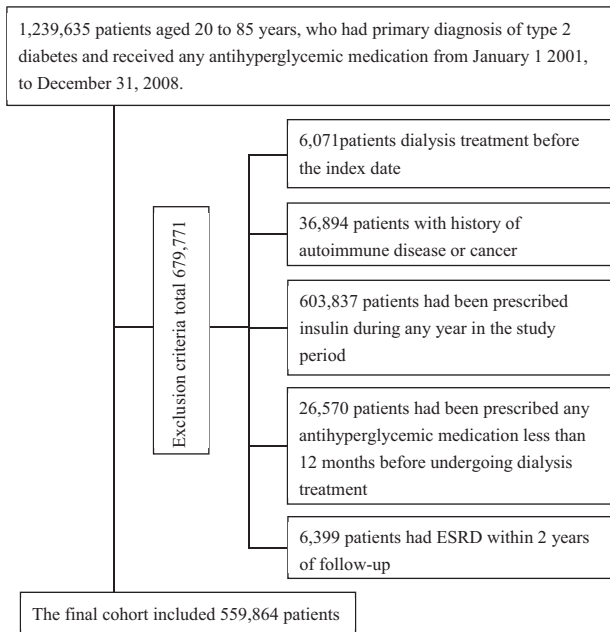


FIGURE 1. . Flow chart of patient selection.

**Statistical Analysis**

The characteristics of cases and controls were compared using the Chi-squared test for categorical variables and Student *t* test for continuous variables. After adjusting for all covariates, we use multivariate Cox proportional hazard regression models to evaluate the association between OAM adherence of time dependence and ESRD onset. Hazard ratio (HR) with 95% confidence interval (CI) was calculated for each independent variable in the multivariable models. We performed a time-dependent analysis of medication adherence since medication adherence is likely to vary over time.<sup>31</sup> Several sensitivity analyses are performed to verify the robustness of our findings. We repeated analyses stratified by antihypertensive medications adherence (MPR < 80% and MPR ≥ 80%) for the association between OAM adherence and occurrence of ESRD. The interactive effects between adherence and CCI on ESRD risk are stratified by age (age ≥ 65 and age < 65) and antihypertensive medication adherence levels (MPR ≥ 80% and MPR < 80%). All analyses and calculations were performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC). Results were considered statistically significant where *P* value < 0.05.

**RESULTS**

**Patient Characteristics**

Figure 1 depicts the patient selection process. The NHIRD contained 1,239,635 patients who had a primary diagnosis of type 2 diabetes and had received antihyperglycemic medications from January 1, 2001 to December 31, 2008. Patients who received dialysis before the diabetes diagnosis (n = 6071), had autoimmune disease or cancer (n = 36,894), had insulin prescriptions during any of the years in the study period (n = 603,837), used OAM < 12 months before receiving dialysis (n = 26,570), and had ESRD in the beginning of the 2 years of follow-up (n = 6399) were excluded.

Table 1 shows baseline characteristics of patients in the study. The mean age of the patients was 56.53 ± 11.56 years, and most of them were men (52.11%). In addition, 1695 (0.30%) patients with ESRD had an average follow-up period of 5.7 years. Compared with the patients without ESRD, those with ESRD were older, male, and had a higher number of comorbidities, including hypertension, gout, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, congestive heart failure, anemia, and CKD. ESRD groups also have higher summary score of CCI than that of non-ESRD group. Regarding pharmacotherapy, 15.69% of ESRD patients and 13.38% of non-ESRD patients were prescribed statins. Patients with ESRD were less likely to undergo antihypertensive polytherapy or metformin monotherapy, but were more likely to undergo OAM polytherapy.

**Effects on Major Kidney Events**

Table 2 shows the HR of ESRD among the patients with diabetes. After adjustment for the covariates, patients who were nonadherent to OAM were associated with a higher risk of ESRD compared with those who were adherent to OAM (HR, 1.11; 95% CI, 1.01–1.23). Furthermore, among the various comorbidities, hypertension, gout, cerebrovascular disease, congestive heart failure, anemia, and CKD were identified as critical risk factors for ESRD. A higher CCI indicated an increased risk of ESRD (HR, 1.16; 95% CI, 1.10–1.22). Patients who were prescribed statins had a significantly higher risk of ESRD compared with those who were not prescribed statins (HR, 1.19; 95% CI, 1.07–1.34). Regarding the prescription of NSAIDs, the risk of ESRD was lower among the patients who were prescribed NSAIDs than among those who were prescribed none (HR, 0.41; 95% CI, 0.37–0.45). Metformin monotherapy was associated with a lower risk of ESRD compared with none-monotherapy (HR, 0.38; 95% CI, 0.29–0.49).

Table 3 shows the HR for ESRD onset for the 3 patient groups (adherent to OAM, CCI ≥ 2; nonadherent to OAM, CCI ≤ 1; nonadherent to OAM, CCI ≥ 2) compared with the reference group (adherent to OAM; CCI ≤ 1). Patients who were adherent to OAM and had a CCI ≥ 2 (HR, 2.09; 95% CI, 1.57–2.77) had a higher risk of ESRD onset compared with the reference group. Furthermore, patients who were nonadherent to OAM and had a CCI ≥ 2 (HR, 3.76; 95% CI, 3.13–4.52) were at a higher risk of ESRD onset (compared with the reference group) than patients who were nonadherent to OAM and had a CCI ≤ 1 (HR, 2.09; 95% CI, 1.80–2.42).

Figure 2 shows a forest plot depicting the association between nonadherence to OAM and ESRD risk according to the multivariate stratified analysis. The figure shows that the effects of nonadherence to OAM on ESRD risk were nonsignificant for ages. Furthermore, patients without hypertension (HR, 1.18; 95% CI, 1.00–1.39), without gout (HR, 1.13; 95% CI, 1.02–1.26), without CKD (HR, 1.17; 95% CI, 1.03–1.33), undergo OAM polytherapy (HR, 1.22; 95% CI, 1.08–1.38), and undergo metformin none-monotherapy (HR, 1.13; 95% CI, 1.02–1.25) were at a higher risk of ESRD onset. Nonadherence to OAM had no significant effect on the risk of ESRD among patients who were adherent to antihypertensive medications. However, nonadherence to OAM increased the risk of ESRD among patients who were also nonadherent to antihypertensive medications.

**TABLE 1.** Baseline Characteristics of ESRD and Non-ESRD Initiating a New Antihyperglycemic Medication

Variable	All Patients (n = 559,864)	ESRD (n = 1695)	Non-ESRD (n = 558,169)	P Value
Age, mean ± SD	56.53 ± 11.56	57.55 ± 11.30	56.53 ± 11.56	<0.001
Age, y				<0.001
20–44	17.04	13.92	17.05	
45–55	31.46	30.86	31.46	
55–65	27.76	28.61	27.76	
≥65	23.74	26.61	23.73	
Gender				<0.001
Male	52.11	63.36	52.08	
Female	47.89	36.64	47.92	
Hypertension	44.61	61.12	44.56	<0.001
Gout	6.01	10.62	5.99	<0.001
Ischemic heart disease	8.68	9.44	8.68	0.2851
Cerebrovascular disease	5.09	8.08	5.08	<0.001
Peripheral arterial disease	0.73	1.12	0.73	0.0776
Congestive heart failure	1.06	2.12	1.06	<0.001
Anemia	0.61	2.54	0.61	<0.001
CKD	3.51	22.42	3.45	<0.001
CCI, mean ± SD	0.49 ± 0.75	0.72 ± 1.04	0.49 ± 0.75	
CCI				<0.001
0	62.86	58.23	62.88	
1	27.66	21.00	27.68	
2	7.24	13.16	7.23	
≥3	2.23	7.61	2.21	
Statin medications				0.006
None-prescribed	86.61	84.31	86.62	
Prescribed	13.39	15.69	13.38	
Antihypertensive medications				0.018
None-prescribed	2.30	1.25	2.31	
Monotherapy	75.75	78.76	75.74	
Polytherapy	21.94	19.98	21.95	
NSAIDs medications				<0.001
None-prescribed	42.98	55.40	42.94	
Prescribed	57.02	44.60	57.06	
OAM				<0.001
Monotherapy	39.16	32.68	39.18	
Polytherapy	60.84	67.32	60.82	
Metformin				<0.001
None-monotherapy	88.23	96.28	88.21	
Monotherapy	11.77	3.72	11.79	

Data expressed as mean ± SD or percentage. CCI = Charlson comorbidity index, CKD = chronic kidney disease, ESRD = end-stage renal disease, NSAIDs = nonsteroidal anti-inflammatory drugs, OAM = oral antihyperglycemic medication, SD = standard deviation.

### Sensitivity Analysis Results

After adjusting for the covariates, we stratified the interactive effects between adherence and the CCI on ESRD risk by age (age ≥ 65 years vs. age < 65 years) and antihypertensive medication adherence level (MPR ≥ 80% vs. MPR < 80%; see Table 4). The results of these sensitivity analyses are identical to those shown in Table 3.

### DISCUSSION

In the present study, we investigated the association between antihyperglycemic medication adherence and the risk of ESRD among patients with newly diagnosed type 2 diabetes. We found that nonadherence to OAM is associated with an increased risk of ESRD compared with adherence to OAM. In

addition, the results indicate that patients who had comorbidities, took statins, received antihypertensive medication polytherapy, received OAM polytherapy, and metformin non-monotherapy had a relatively higher risk of ESRD onset, after adjusted for various covariates. These results are in agreement with those of numerous previous studies related to kidney disease.<sup>2–6,18,32,33</sup>

However, in the present study, being prescribed NSAIDs had no effect on the risk of ESRD onset, which is unsurprising. Previous studies have shown that regular NSAIDs use does not increase the risk of accelerated CKD progression.<sup>34–36</sup> Nderitu et al<sup>34</sup> proposed that high doses of NSAIDs use results in the increase of the risk which accelerates renal function decline. A possible explanation is that our data were assessed at the baseline and not throughout the study period.

**TABLE 2.** Crude and Adjusted Hazard Ratio of ESRD Among Patients With Type 2 Diabetes

Outcome	Crude HR (95% CI)	Adjusted HR <sup>†</sup> (95% CI)
OAM adherence level*		
Adherent (MPR ≥ 80%)	Reference	Reference
Nonadherent (MPR < 80%)	1.07 (0.96–1.18)	1.11 (1.01–1.23)
Age, y		
20–45	0.90 (0.77–1.05)	0.97 (0.83–1.14)
45–55	Reference	Reference
56–65	1.01 (0.89–1.15)	0.95 (0.84–1.08)
≥65	1.16 (1.02–1.31)	0.89 (0.78–1.02)
Gender		
Male	Reference	Reference
Female	0.60 (0.54–0.66)	0.64 (0.58–0.71)
Hypertension	2.09 (1.89–2.30)	2.10 (1.90–2.31)
Gout	2.16 (1.85–2.52)	1.57 (1.34–1.84)
Ischemic heart disease	1.56 (0.98–1.36)	0.86 (0.73–1.02)
Cerebrovascular disease	1.88 (1.58–2.24)	1.39 (1.16–1.67)
Peripheral arterial disease	1.70 (1.08–2.67)	1.15 (0.73–1.81)
Congestive heart failure	2.62 (1.88–3.65)	1.82 (1.29–2.55)
Anemia	6.81 (5.45–8.52)	5.85 (4.66–7.34)
CKD	9.96 (9.10–10.90)	7.94 (7.17–8.80)
CCI	1.40 (1.33–1.47)	1.16 (1.10–1.22)
Statin medications		
None-prescribed	Reference	Reference
Prescribed	1.32 (1.18–1.48)	1.19 (1.07–1.34)
NSAIDs medications		
None-prescribed	Reference	Reference
Prescribed	0.45 (0.41–0.49)	0.41 (0.37–0.45)
OAM		
Monotherapy	Reference	Reference
Polytherapy	1.15 (1.04–1.28)	0.95 (0.86–1.06)
Metformin		
None-monotherapy	Reference	Reference
Monotherapy	0.40 (0.31–0.52)	0.38 (0.29–0.49)

CCI = Charlson comorbidity index, CI = confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, HR = hazard ratio, MPR = medication possession ratio, NSAIDs = nonsteroidal anti-inflammatory drugs, OAM = oral antihyperglycemic medication.

\* Time-dependent OAM adherence level for estimating the risk of ESRD.

† Adjusted for covariate factors, including age, gender, hypertension, gout, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, congestive heart failure, anemia, CKD, CCI, Statin medications, NSAIDs medications, OAM, and metformin.

Our stratified analyses revealed that without CKD has a significant effect on ESRD onset, which is consistent with previous research on antihypertensive medication adherence.<sup>18</sup> Our results also show that multiple therapies by

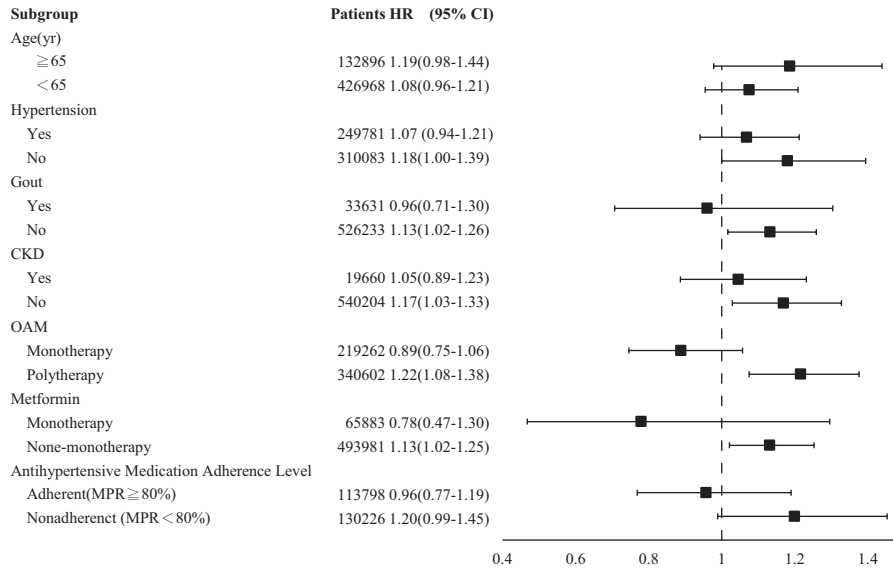
OAM and metformin none-monotherapy are strong predictive factors for ESRD onset. Similar to other studies, the number of drugs used for antihypertensive treatment was associated with an increased risk of ESRD onset.<sup>18</sup> In other

**TABLE 3.** Interactive Effects Between Charlson Comorbidity Index and Adherence on ESRD Risk

Adherence	CCI	Non-ESRD		ESRD		Crude HR (95% CI)	Adjusted HR* (95% CI)
		N	%	N	%		
Adherent	≤1	165,339	29.62	210	12.39	Reference	Reference
Adherent	≥2	18,422	3.30	64	3.78	2.91 (2.20–3.85)	2.09 (1.57–2.77)
Nonadherent	≤1	340,150	60.94	1133	66.84	2.04 (1.76–2.37)	2.09 (1.80–2.42)
Nonadherent	≥2	34,258	6.14	288	16.99	5.27 (4.41–6.30)	3.76 (3.13–4.52)

CCI = Charlson comorbidity index, CI = confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, HR = hazard ratio, NSAIDs = nonsteroidal anti-inflammatory drugs, OAM = oral antihyperglycemic medication.

\* Adjusted for covariate factors, including age, gender, hypertension, gout, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, congestive heart failure, anemia, CKD, CCI, Statin medications, NSAID medications, OAM, and metformin.



**FIGURE 2.** Multivariable stratified analyses and adjusted HR\* for the association between OAM nonadherent (MPR < 80%)<sup>†</sup> and ESRD. CCI = Charlson comorbidity index, CKD = chronic kidney disease, CI = confidence interval, ESRD = end-stage renal disease, HR = hazard ratio, MPR = medication possession ratio, NSAIDs = nonsteroidal anti-inflammatory drugs, OAM = oral antihyperglycemic medication. \*Multivariable analysis is by Cox proportional hazards model. Adjusted for covariate factors, including age, gender, hypertension, gout, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, congestive heart failure, anemia, CKD, CCI, Statin medications, antihypertensive medications, NSAIDs medications, OAM, and metformin. <sup>†</sup>Time-dependent antihyperglycemic medication nonadherence for estimating the risk of ESRD.

words, the higher the severity of diabetes is the higher the risk of ESRD.

Prior to the onset of diabetes, the interactive effects of adherence and the CCI significantly affected the patients' risk of ESRD. Patients who were nonadherent to OAM and had severe comorbidities were at a relatively higher risk of ESRD onset. Previous studies have shown that comorbidities are risk factors for ESRD,<sup>5,6</sup> indicating that adherence to OAM can mitigate a decline in renal function. As argued by a study conducted in Canada, high adherence to antihypertension medication markedly reduces the risk of ESRD.<sup>18</sup> These findings were consistent in the sensitivity analyses after stratification by age and antihypertensive medication adherence and adjustment for age, sex, comorbidity, and medication use (Table 4).

The strength of the present study is that it involved a large research sample from a comprehensive nationwide database representing current practice patterns. Our selection criteria allowed only patients with newly diagnosed diabetes between 2001 and 2008 to be included in the study, thereby excluding the potential biases. For example, the patients discontinued use the diabetes drug because of the adverse effects of drugs or death.

Previous studies have shown that high OAM adherence effectively prevents CVD and cerebrovascular outcome.<sup>19–21</sup> Moreover, antihypertensive medication adherence has been significantly associated with a decreased risk of ESRD.<sup>18</sup> According to our research, no study has addressed the effect of antihyperglycemic medication adherence on ESRD onset.

**TABLE 4.** Interactive Effects Between Charlson Comorbidity Index and Adherence on ESRD Risk Stratified by Age and Antihypertensive Medication Adherence Level

Adherence	CCI	Age ≥ 65	Age < 65	Adherent (MPR ≥ 80%)	Nonadherent (MPR < 80%)
		HR* (95% CI)	HR* (95% CI)	HR <sup>†</sup> (95% CI)	HR <sup>†</sup> (95% CI)
Adherent	≤1	Reference	Reference	Reference	Reference
Adherent	≥2	1.56 (0.99–2.45)	2.43 (1.69–3.49)	1.23 (0.67–2.27)	2.53 (1.69–3.77)
Nonadherent	≤1	1.41 (1.09–1.82)	2.45 (2.04–2.94)	1.57 (1.18–2.10)	2.19 (1.73–2.78)
Nonadherent	≥2	3.02 (2.24–4.08)	4.10 (3.25–5.17)	2.30 (1.60–3.31)	4.37 (3.29–5.82)

CCI = Charlson comorbidity index, CI = confidence interval, CKD = chronic kidney disease, ESRD = end-stage renal disease, HR = hazard ratio, MPR = medication possession ratio, NSAIDs = nonsteroidal anti-inflammatory drugs, OAM = oral antihyperglycemic medication.

\*Adjusted for covariate factors, including gender, hypertension, gout, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, congestive heart failure, anemia, CKD, Statin medications, NSAIDs medications, OAM, and metformin.

<sup>†</sup>Adjusted for covariate factors, including age, gender, gout, ischemic heart disease, cerebrovascular disease, peripheral arterial disease, congestive heart failure, anemia, CKD, Statin medications, NSAIDs medications, OAM, and metformin.

This study is the first to provide empirical evidence demonstrating the effects of antihyperglycemic medication on ESRD onset.

Most previous studies related to antihyperglycemic medication adherence have analyzed the follow-up period,<sup>28,37,38</sup> but they used an MPR that was calculated according to the length of the follow-up period. In this study, we performed a time-dependent analysis of OAM adherence and ESRD. Immortal time bias, immeasurable time bias, and changes in drug consumption over time were considered in our research methodology.

Three main limitations were encountered while conducting this study. First, the NHIRD does not contain information on several potential confounding factors, including socioeconomic status, smoking, alcohol consumption, lifestyle, obesity, family history, genetic factors, and environmental exposure. Furthermore, we did not consider the potential effects of biochemical data, such as cholesterol, glucose, insulin, and glycated hemoglobin levels. Because we could not obtain information on the exact levels of glycemic control, the relationships between ESRD and severity of diabetes could not be further assessed. Instead, we used the type of OAM (metformin and nonmetformin) and number of OAMs to indicate the severity of diabetes.

Second, we used prescription refill patterns to assess adherence to OAM. Because ascertaining realistic information based on the medications that patients have taken is difficult, using the MPR to measure medication adherence might have resulted in an overestimate of their actual drug consumption.<sup>38,39</sup> The MPR is a common measure used in pharmacy claims data for determining patient medication adherence. Thus, this study used the definition of the MPR < 80% proposed by previous studies to determine whether patients were non-adherent.<sup>18,27,28,40</sup> Previous studies have demonstrated that adherence estimates that were obtained using pharmacy claims data are closely related to the clinical outcome measures.<sup>38,39</sup>

Third, participants in this study consisted solely of non-insulin dependent diabetes patients; this may point to a study population whose diabetes was less severe. The results may limit the generalization for patients with diabetes.

In conclusion, this study found that nonadherence to OAM therapy is related to ESRD onset. After patients with severe comorbidities develop diabetes, they should adhere to their prescribed antihyperglycemic medication to reduce the risk of ESRD. In other words, enhancing medication adherence can effectively reduce the risk of declining renal function. Therefore, we recommend that clinicians educate their patients regarding medication adherence and the importance of taking prescribed medications as instructed. Accordingly, patients should strictly control their blood sugar levels and regularly evaluate their medication adherence. Furthermore, we recommend that researchers, managers of medical facilities, and policy makers develop strategies and clinical interventions for patients who are nonadherent to their medication regimens. In summary, adherence to drug therapy can facilitate preventing the progressive loss of renal function and development of ESRD among patients with diabetes. In addition, it can facilitate reducing the overall cost of dialysis treatment and alleviating the associated national social and financial burdens.

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