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.

(Internat Med 94(47):e2051)
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. 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.

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, sulfonylureas, a-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptide 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. 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; 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 follow for a minimum of 12 months to a maximum of 7 years.

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 anti-hypertensive 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 comonitmate diseases defined by the ICD-9-CM, was used in this study. We also considered the effect of the type of antihyperglycemic treatment. To measure 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 of 0; patients who adhered to OAM with a CCI of 1 (reference group); patients who did not adhere to OAM with a CCI of 1; and patients who did not adhere to OAM with a CCI of 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.

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. 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 denying receive the treatment of medications; this might produce misleading results regarding the effect of treatment adherence.
1,239,635 patients aged 20 to 85 years, who had primary diagnosis of type 2 diabetes and received any antihyperglycemic medication from January 1, 2001, to December 31, 2008.

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, 7.36; 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.
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 nonmonotherapy 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.2–6,18,32,33

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.34–36 Nderitu et al34 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 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                    |                           |                 |                       | <0.001  |
| Gout                            | 6.01                      | 10.62           | 5.99                  |         |
| 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           | <0.001  |
| 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.
Our stratified analyses revealed that without CKD has a significant effect on ESRD onset, which is consistent with previous research on antihypertensive medication adherence.18 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.18 In other

### Table 2. Crude and Adjusted Hazard Ratio of ESRD Among Patients With Type 2 Diabetes

| Outcome                                | Crude HR (95% CI) | Adjusted HR† (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                | 1.85 (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.

† 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.

### 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) |
|-----------|-----|----------|------|-------------------|-----------------------|
| Adherent  | ≤1  | 165,339  | 29.62| Reference         | Reference             |
|           | ≥2  | 18,422   | 3.30 | 2.91 (2.20–3.85)  | 2.09 (1.57–2.77)      |
| Nonadherent| ≤1 | 340,150  | 60.94| 66.84             | 2.04 (1.76–2.37)      |
|           | ≥2 | 34,258   | 6.14 | 16.99             | 5.27 (4.41–6.30)      |

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.
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, 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. 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. Moreover, antihypertensive medication adherence has been significantly associated with a decreased risk of ESRD. 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

| Subgroup | Patients HR (95% CI) |
|----------|----------------------|
| Age(yr)  |                      |
| ≥65      | 1.19 (0.98–1.44)     |
| <65      | 1.08 (0.96–1.21)     |
| Hypertension |                  |
| Yes      | 1.07 (0.94–1.21)     |
| No       | 1.18 (1.00–1.39)     |
| Gout     |                      |
| Yes      | 0.71 (0.61–1.30)     |
| No       | 1.12 (1.02–1.26)     |
| CKD      |                      |
| Yes      | 0.89 (0.89–1.23)     |
| No       | 1.17 (1.03–1.33)     |
| OAM      |                      |
| Monotherapy | 0.89 (0.75–1.06)    |
| Polytherapy | 1.22 (1.08–1.38)    |
| Metformin|                      |
| Monotherapy | 0.78 (0.47–1.30)    |
| None-monotherapy | 1.13 (0.82–1.55) |

CCI = Charlson comorbidity index, CI = confidence interval, 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 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.

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### FIGURE 2. Multivariable stratified analyses and adjusted HR for the association between OAM nonadherence (MPR < 80%) and ESRD.

CCI = Charlson comorbidity index, CI = confidence interval, 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 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.

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Previous studies have shown that high OAM adherence effectively prevents CVD and cerebrovascular outcome. Moreover, antihypertensive medication adherence has been significantly associated with a decreased risk of ESRD. According to our research, no study has addressed the effect of antihyperglycemic medication adherence on ESRD onset.
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, 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. 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 nonadherent. Previous studies have demonstrated that adherence estimates that were obtained using pharmacy claims data are closely related to the clinical outcome measures.

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.

REFERENCES
1. U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States Bethesda, MD: USRDS; 2013.
2. Stefanadis CI. Complex interrelationships between heart and kidneys: establishing the role of cardiorenal syndrome. Hellenic J Cardiol. 2010;51:87–88.
3. Kahn MR, Robbins MJ, Kim MC, et al. Management of cardiovascular disease in patients with kidney disease. Nat Rev Cardiol. 2013;10:261–273.
4. Sozio SM, Armstrong PA, Coresh J, et al. Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study. Am J Kidney Dis. 2009;54:468–477.
5. Drakoulougkona O, Barbulescu AL, Rica I, et al. The outcome of patients with lupus nephritis and the impact of cardiovascular risk factors. Curr Health Sci J. 2011;37:70–74.
6. Malekmakan L, Haghpanah S, Pakefrat M, et al. Causes of chronic renal failure among Iranian hemodialysis patients. Saudi J Kidney Dis Transpl. 2009;20:501–504.
7. Assogba FG, Coughoud C, Hamedouche T, et al. Trends in the epidemiology and care of diabetes mellitus-related end-stage renal disease in France, 2007–2011. Diabetologia. 2014;57:718–728.
8. Virginia LP, Benat M, Jesus E, Carmen GG. Immunoinflammation in Diabetic Nephropathy: Molecular Mechanisms and Therapeutic Options, Diabetic Nephropathy. In: Chan J, ed. ISBN: 978-953-51-0453-5. InTech; 2012. http://www.intechopen.com/books/diabeticnephropathy/immunoinflammation-in-diabetic-nephropathy-molecular-mechanisms-and-therapeutic-options. Accessed May 5, 2015.
9. Perkovic V, Heerspink HL, Chalmers J, et al. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int. 2013;83:517–523.
10. Coca SG, Ismaiel-Beigi F, Haq N, et al. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med. 2012;172:761–769.
11. Levin SR, Coburn JW, Abraira C, et al. Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators. Diabetes Care. 2000;23:1478–1485.
12. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–2559.
13. Hearnsaw H, Lindemeyer A. What do we mean by adherence to treatment and advice for living with diabetes? A review of the literature on definitions and measurements. Diabet Med. 2006;23:720–729.
14. Cramer JA. A systematic review of adherence with medications for diabetes. Diabetes Care. 2004;27:1218–1224.
15. Debuschke I. Is adherence a relevant issue in the self-management education of diabetes? A mixed narrative review. Diabetes Metab Syndr Obes. 2014;7:357–367.
16. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication adherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med. 2006;166:1836–1841.
17. Sokol MC, McGuigan KA, Verbrugge RR, et al. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. 2005;43:521–530.
18. Roy L, White-Guay B, Dorais M, et al. Adherence to antihypertensive agents improves risk reduction of end-stage renal disease. Kidney Int. 2013;84:570–577.
19. Broadbent E, Donkin L, Stroh JC. Illness and treatment perceptions are associated with adherence to medications, diet, and exercise in diabetic patients. Diabetes Care. 2011;34:338–340.
20. Boswell KA, Cook CL, Burch SP, et al. Associating medication adherence with improved outcomes: a systematic literature review. *Am J Pharm Benefits*. 2012;4:e97–e108.

21. Asche C, LaFleur J, Conner C. A review of diabetes treatment adherence and the association with clinical and economic outcomes. *Clin Ther*. 2011;33:74–109.

22. Lin CF, Liu JC, Chi NF, et al. The effect of osteoarthritis on 1-year risk of ischemic heart disease following total knee arthroplasty. *J Arthroplasty*. 2014;29:2447–2451.

23. Cheng TM. Taiwan’s new national health insurance program: genesis and experience so far. *Health Affair*. 2003;22:61–76.

24. Chi NF, Chien LN, Ku HL, et al. Alzheimer disease and risk of stroke: a population-based cohort study. *Neurology*. 2013;80:705–711.

25. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010;33 (suppl 1):S62–S69.

26. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Diabetes Care*. 2004;27:2149–2153.

27. Chen CC, Tseng CH, Cheng SH. Continuity of care, medication adherence, and health care outcomes among patients with newly diagnosed type 2 diabetes: a longitudinal analysis. *Med Care*. 2013;51:231–237.

28. Adeyemi AO, Rascati KL, Lawson KA, et al. Adherence to oral antidiabetic medications in the pediatric population with type 2 diabetes: a retrospective database analysis. *Clin Ther*. 2012;34:712–719.

29. Garay-Sevilla ME, Porras JS, Malacara JM. Coping strategies and adherence to treatment in patients with type 2 diabetes mellitus. *Rev Invest Clin*. 2011;63:155–161.

30. Gregoire SMJH, Jager HR, Yousry TA, et al. Brain microbleeds as a potential risk factor for antplatelet-related intracerebral haemorrhage: hospital-based, case-control study. *J Neurol Neurosurg Psychiatry*. 2010;81:679–684.

31. An JJ, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care*. 2013;51:879–887.

32. Murea M. Advanced kidney failure and hyperuricemia. *Adv Chronic Kidney Dis*. 2012;19:419–424.

33. Minutolo R, Lapi F, Chiodini P, et al. Risk of ESRD and death in patients with CKD not referred to a nephrologist: a 7-year prospective study. *Clin J Am Soc Nephrol*. 2014;9:1586–1593.

34. Oladapo AO, Barner JC, Rascati KL, et al. A retrospective database analysis of neuropathic pain and oral antidiabetic medication use and adherence among Texas adults with type 2 diabetes enrolled in Medicaid. *Clin Ther*. 2012;34:605–613.

35. Hess LM, Raebel MA, Conner DA, et al. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother*. 2006;40:1280–1288.

36. Hong JS, Kang HC. Relationship between continuity of ambulatory care and medication adherence in adult patients with type 2 diabetes in Korea: a longitudinal analysis. *Med Care*. 2014;52:446–453.