Association of renal and cardiovascular safety with DPP-4 inhibitors vs sulfonylureas in type 2 diabetes patients with advanced chronic kidney disease

Chun-Ting Yang, MS[1]
Wei-Hung Lin, MD, PhD[2,3]
Lun-Jie Li, MS[1]
Huang-Tz Ou, PhD[1,4,5]
Shihchen Kuo, RPh, PhD[6]

Author Affiliations:

[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[2]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[3]Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[4]Department of Pharmacy, College of Medicine, National Cheng Kung University, Tainan, Taiwan
[5]Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan
[6]Division of Metabolism, Endocrinology & Diabetes, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, United States

Corresponding Author:

Huang-Tz Ou, PhD

Institute of Clinical Pharmacy and Pharmaceutical Sciences
College of Medicine, National Cheng Kung University
1 University Road
Tainan 701, Taiwan
Telephone: 886-6-2353535 ext.5685
Fax: 886-6-2373149
Email: huangtz@mail.ncku.edu.tw

Funding:
This project was supported by grants from the Ministry of Science and Technology in Taiwan (grant MOST 109-2320-B-006-047-MY3) (Huang-Tz Ou). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of interest
The authors declared no competing interests for this work.

Keywords: advanced chronic kidney disease, cardiovascular safety, dipeptidyl peptidase-4 inhibitors, heart failure, renal safety, sulfonylureas, type 2 diabetes.

Abstract

This study assessed the effects of dipeptidyl peptidase-4 inhibitors (DPP4is) versus sulfonylureas (SUs) on composite renal, cardiovascular, and hospitalized hypoglycemia outcomes in type 2 diabetes (T2D) patients with advanced chronic

kidney disease (CKD) who were under-represented in previous clinical studies. The National Health Insurance Research Database was utilized. Patients with T2D and advanced CKD (stages 3b-5) with stable use of DPP4is or SUs were identified during 2011-2015 and followed until death or December 31, 2016. The primary outcome was the composite renal outcome. Secondary outcomes included hospitalized heart failure (HHF), major adverse cardiovascular event (MACE), hospitalized hypoglycemia, and all-cause death. Subdistribution hazard models were employed to assess treatment effects on clinical outcomes. A total of 1,204 matched pairs of DPP4i and SU users were analyzed. Compared with SUs, DPP4is had no significant difference in the risks of the composite renal outcome, HHF, and three-point and four-point MACE (hazard ratios [95% CIs]: 1.10 [0.93-1.31], 1.11 [0.95-1.30], 0.97 [0.79-1.19], and 1.08 [0.94-1.24], respectively), but reduced risks of hospitalized hypoglycemia (0.53 [0.43-0.64]) and all-cause death (0.71 [0.53-0.96]). In conclusion, among T2D patients with advanced CKD, the use of DPP4is versus SUs was associated with comparable safety profiles on renal and cardiovascular outcomes, and reduced risks of hospitalized hypoglycemia and all-cause death. DPP4is may be preferred for T2D patients with advanced CKD, and the regular monitoring on cardiac function remains crucial among this population who are at a higher risk of HHF.

Introduction

Chronic kidney disease (CKD) is a prevalent comorbidity among patients with type 2 diabetes (T2D) across countries (25-40%),[1-4] creating immense health and economic burdens on individuals, healthcare systems, and societies. The selection of an appropriate glucose-lowering therapy for T2D patients with CKD, especially those with advanced CKD (stages 3b-5, estimated glomerular filtration rate [eGFR] of <45 mL/min/1.73m^2), has been challenging because such patients are more vulnerable to

adverse effects of glucose-lowering agents (GLAs) such as hypoglycemia, lactic acidosis, and cardiovascular diseases (CVDs).

Additional barriers have cautioned or limited the use of GLAs in this population. Among conventional GLAs, metformin is contraindicated for patients with an eGFR of <30 mL/min/1.73m^2 due to an increased risk of lactic acidosis. Thiazolidinediones increase the risk of heart failure (HF), and are thus not recommended for CKD populations [5,6] who are susceptible to HF.[7] Alpha-glucosidase inhibitors are generally not considered as a first-line agent for CKD patients because of limited data regarding their long-term safety and efficacy. Insulins are not preferred in a front-line setting for CKD patients because the close monitoring of blood glucose levels and frequent adjustment of insulin doses are needed. Among novel GLAs, sodium-glucose cotransporter 2-inhibitors are not approved for patients with an eGFR of <30 mL/min/1.73m^2. The safety profile of glucagon-like peptide-1 receptor agonists in patients with CKD is uncertain,[8] and patients may hesitate to use them because of their high costs and injectable formulation. The therapeutic options for glucose-lowering treatment for T2D patients with advanced CKD may thus be limited to sulfonylureas (SUs), meglitinides, and dipeptidyl peptidase-4 inhibitors (DPP4is). DPP4is and SUs are the two most commonly prescribed GLAs for patients with CKD (Figure S1). In this population, DPP4is are generally preferable because of their relatively low risk of hypoglycemia and neutral cardiovascular effects.[5,6] SUs are low-cost alternatives but require the close blood glucose monitoring due to an increased risk of hypoglycemia.[9]

T2D patients with advanced CKD have been under-represented in previous studies on the assessment of safety outcomes associated with DPP4is, including both clinical trials of patients with established CVDs or at high risk for CVDs[10-17] and real-world studies on general T2D populations.[18-21] To date, no studies have evaluated

the association between DPP4is and major renal and cardiovascular outcomes in T2D patients with advanced CKD.[8] Against this background, we assessed the association of DPP4is versus SUs with renal, cardiovascular, and hospitalized hypoglycemic outcomes among T2D patients with advanced CKD to inform clinical decision-making of glucose-lowering treatment for this population.

Methods

Data source

This retrospective cohort study utilized Taiwan's National Health Insurance Research Database (NHIRD) 2007-2016. The NHIRD is a nationwide population-based database in which all reimbursed medical services of enrollees in the National Health Insurance (NHI) program were documented.[22] This study was approved by the Institutional Review Board of National Cheng Kung University (A-EX-106013).

Cohort identification

People with T2D in the NHIRD 2008-2015 were included and then those with advanced CKD (stages 3b-5) were identified by confirming the enrollment status in the national pre-end stage renal disease (pre-ESRD) pay-for-performance program, which was officially launched by the NHI program to improve the healthcare quality for patients with advanced CKD and alleviate their disease progression to ESRD and chronic dialysis.[23] Among these selected T2D patients with advanced CKD, the stable users of DPP4is or SUs (i.e., having at least three sequential refills of DPP4is or SUs with refilling gaps less than 30 days) in 2011-2015 were further identified. The date for the stable use of a study drug being confirmed (i.e., the third refill of the study

drug) was defined as the index date. The operational definitions of abovementioned cohort identification criteria are detailed in Table S1.

Patients with histories of chronic dialysis, kidney transplant, or erythropoiesis-stimulating agent (ESA) use in the year before or at the index date were further excluded. According to the NHI reimbursement policy, ESA is reimbursed for CKD patients with a serum creatinine level of >6.0 mg/dL (approximately equivalent to CKD stage 5) and hematocrit of <28%.[24] ESA use was applied as an exclusion criterion to minimize the heterogeneity of the study cohort. A flowchart of the study cohort selection is illustrated in Figure 1.

The study cohort of T2D patients with advanced CKD may have been exposed to multiple GLAs before using DPP4is or SUs. The incident new-user cohort design, which considers only incident new users (treatment-naïve patients to DPP4is or SUs), would include a relatively small fraction of real-world patients and thus limit the study generalizability to routine clinical diabetes care. Therefore, we adopted the prevalent-user cohort design[25] to include not only incident users but also prevalent users of DPP4is or SUs, which would reflect a representative of real-life patients in clinical settings.

Furthermore, a two-step matching algorithm was implemented to enhance the comparability between study groups of DPP4i and SU users.[25] First, the previous utilization patterns of GLAs were considered as an important proxy for patients' underlying status of diabetes management and therefore utilized as the matching criterion. Specifically, patients exposed to the same number of GLA classes were matched first, with a maximum 90-day drug supply difference (±45 days) of prior use of DPP4is or SUs allowed for the matched pairs. Second, 1:1 nearest neighbor propensity score matching was used to adjust for the imbalanced baseline patient characteristics between study groups. The propensity score was estimated using a

logistic regression model where treatment status (DPP4is versus SUs) was fitted with a variety of demographic and clinical characteristics (Table 1) relevant to either treatment selection or study outcomes.

Definitions of treatment exposure and study outcomes

Exposure to GLAs was measured using the World Health Organization Anatomical Therapeutic Chemical Classification system. The primary outcome was the composite renal outcome of chronic dialysis (defined as dialysis therapy for >90 days) or kidney transplant, which were ascertained from the Registry for Catastrophic Illness Patients file in the NHIRD. Secondary outcomes included 1) hospitalized heart failure (HHF), 2) a three-point major adverse cardiovascular event (3P-MACE), namely non-fatal myocardial infarction or stroke or fatal CVD, 3) a four-point major adverse cardiovascular event (4P-MACE), namely HHF or 3P-MACE, 4) hospitalized hypoglycemia, and 5) all-cause death. Cardiovascular outcomes and hypoglycemia were measured from inpatient and emergency department records of NHI claims data using International Classification of Disease, Ninth revision, Clinical Modification and International Classification of Disease, Tenth revision, Clinical Modification disease codes (Table S1).[22] Mortality status and death causes were confirmed from the Cause of Death Data in the NHIRD. Each patient was followed from the index date until the occurrence of study outcomes, death, loss of follow-up, or December 31, 2016, whichever came first (intention-to-treat scenario).

Statistical analyses

Baseline patient characteristics were measured in the year before or at the initiation of study drugs. Differences in baseline characteristics between study groups

were tested using the standardized difference, where an absolute value of <0.1 implies well-balanced characteristics.[26,27]

Considering the relatively high mortality in patients with advanced CKD, subdistribution hazard models, which account for the competing risk of death were employed to estimate the relative risk of study outcomes with using DPP4is versus SUs.[28,29] Subgroup analyses for the primary composite renal outcome were performed by examining interaction terms of treatment status (DPP4is versus SUs) and clinical characteristics (Figure S2) as covariates in the models. Further, comparisons of individual DPP4is (sitagliptin, vildagliptin, saxagliptin, and linagliptin) versus SUs were conducted to explore the variation of treatment effects on study outcomes by DPP4i. Finally, five additional sensitivity analyses were performed to corroborate the robustness of our findings, including 1) use of (a) the classic Cox models and (b) cause-specific hazard models to estimate the relative hazards of DPP4is versus SUs on study outcomes, and 2) reiteration of primary analyses based on (a) as-treated scenario, (b) incident new-user cohort design, and (c) re-defining the index date as the date of the first prescription of a study drug to better reflect the real-world situation where the assessment of treatment-related outcomes generally starts at the treatment initiation (Table S2). A two-tailed *p*-value of <0.05 was considered a statistically significant difference. All analyses were performed using SAS software version 9.4.

Results

A total of 1,204 matched pairs of DPP4i and SU users were included in primary analyses. After matching, study groups were well-balanced (SMD <0.1), except for a slightly higher proportion of dyslipidemia among SU users (Table 1). The average follow-up length was 2.75 and 2.82 years for DPP4i and SU users, respectively.

Given adjustment for the competing risk of death using subdistribution hazard models (Table 2), there were non-significant differences in renal and cardiovascular outcomes between the groups. The subdistribution hazard ratios (SDHRs) and 95% confidence intervals (CIs) of DPP4is versus SUs were 1.10 (0.93-1.31) for the primary renal outcome, 1.11 (0.95-1.30) for HHF, 0.97 (0.79-1.19) for 3P-MACE, and 1.08 (0.94-1.24) for 4P-MACE. There were significantly lower risks of hospitalized hypoglycemia (SDHR: 0.53 [0.43-0.64]) and all-cause death (0.71 [0.53-0.96]) associated with DPP4is versus SUs. In subgroup analyses for the primary renal outcome (Figure S2), no significant interactions were observed, except for the absence versus presence of prior retinopathy history. Results of sensitivity analyses (Table S2) were generally consistent with those of primary analyses, except for no significant difference in all-cause mortality between DPP4i and SU use under the as-treated scenario analysis, incident new-user design analysis, and scenario analysis where the index date was re-defined as the date of initiation of a study drug (sensitivity analyses 3, 4, and 5, respectively), and a significantly increased HHF risk associated with DPP4is versus SUs when the index date was re-defined as the date of initiation of a study drug (sensitivity analysis 5).

Results of the treatment effects of individual DPP4is versus SUs on study outcomes were similar with those in primary analyses (Figure 2 and Table S3), except for a significantly higher HHF risk associated with vildagliptin versus SU use (SDHR: 1.64 [1.02-2.64]) and no significant difference in hospitalized hypoglycemia risk between saxagliptin and SU use (SDHR: 0.62 [0.34-1.12]).

Discussion

This is the first population-based study to assess the comparative safety of the two most commonly prescribed GLAs, namely DPP4is and SUs, in real-world T2D

patients with advanced CKD, who are susceptible to GLA-related adverse effects (e.g., HHF, hypoglycemia) but under-represented in the majority of existing clinical trials and real-world studies. Our study revealed that compared with SUs, the use of DPP4is among T2D patients with advanced CKD had comparable safety profiles on renal and cardiovascular outcomes, and was associated with a considerably lower risk of hospitalized hypoglycemia and possibly a reduced all-cause mortality. Heterogeneity of HHF risks may exist among different DPP4is; that is, a significantly increased HHF risk associated with the use of vildagliptin versus SUs was found, but not in sitagliptin, saxagliptin, or linagliptin.

Renal safety of DPP4is in T2D patients with advanced CKD

The renal safety of DPP4is versus SUs among T2D patients with advanced CKD has not been fully evaluated in the literature. Two cardiovascular outcome trials (CVOTs) consisting of patients with high CVD and/or renal risks assessed the effect of DPP4is on renal outcome as the secondary exploratory end point.[17,30] The SAVOR-TIMI 53 trial reported a non-significant difference in the composite renal outcome of the doubling of creatinine level, initiation of dialysis, kidney transplant, or creatinine >6.0 mg/dL for saxagliptin versus placebo.[30] The post-hoc analysis of the CARMELINA trial showed that across eGFR levels, the use of linagliptin versus placebo yielded a comparable composite renal outcome of ESRD, sustained ≥40% decrease in eGFR from baseline, or renal death.[17] However, these analyses included a limited fraction of patients with advanced CKD, and used a placebo as the comparator. Two real-world studies examined the comparative effectiveness of DPP4is and SUs on risk of renal outcomes among T2D patients.[21,31] Kim et al. reported a non-significantly different risk of ESRD for DPP4is versus SUs.[21] However, a small number of events (17 ESRD events) and a short follow-up period (around 1.6 years)

may affect the study validity, and less than 2% of study patients had CKD, which would greatly limit the study generalizability to the CKD population. Xie et al. reported that in subgroup analyses, there was a non-significantly different risk of the composite outcome of ESRD, eGFR decline >50%, or all-cause mortality for DPP4is versus SUs among T2D patients with advanced CKD.[32] To our best knowledge, our study is the first of its kind to specifically target T2D patients with advanced CKD for assessing renal outcomes of DPP4is. We thus extended current evidence to demonstrate that the use of DPP4is versus SUs was associated with a comparable renal safety profile among T2D patients with advanced CKD.

HHF risks of DPP4is in T2D patients with advanced CKD

Current evidence on the HHF risk of DPP4is in T2D patients with advanced CKD remains limited and yields inconclusive results. In large CVOTs, an increased HHF risk associated with DPP4is has been noticed, including a statistically higher HHF risk of saxagliptin versus placebo in SAVOR-TIMI 53,[10] and a non-significantly increased HHF risk of alogliptin versus placebo in EXAMINE[12] and of linagliptin versus glimepiride in CAROLINA;[16] however, only few patients with advanced CKD were included in these trials. In contrast, the secondary analysis of the CARMELINA trial reported that there was a non-significantly lower HHF risk of linagliptin versus placebo among T2D patients with advanced CKD.[17]

Among real-world studies of T2D patients with renal impairment, two studies reported a significantly higher HHF risk associated with DPP4is versus other GLAs[32] or non-users[33], while three other studies reported a non-significant difference in HHF risk between DPP4i users and non-users.[34-36] However, the interpretation of these study findings should be cautious. First, utilizing a comparison group of non-DPP4i users who were exposed to other types of GLAs would introduce the heterogeneity of

medication effects. Second, although the competing risk of death is an important methodological concern in CKD patients who are at high mortality risk, it was not adjusted in analyses of previous studies. Third, the relatively short follow-up period, ranging from 1 to 1.6 years, in previous studies may limit the applicability of study findings to advanced CKD patients who generally require long-term management. Fourth, these studies were all conducted using study cohorts identified in 2009-2012 when not all DPP4is (e.g., linagliptin) were available on the market and when little was known about the effectiveness and safety of individual DPP4is versus other GLAs. Given the evolution of treatment strategies, studies from earlier periods are of limited value for supporting modern practice. To overcome these limitations, we utilized a cohort identified in a recent period (2011-2015), applied the active-comparator design, and adjusted for the competing risk of death to enhance the validity and generalizability of study findings to current practice.

Our primary analysis and several sensitivity analyses showed no significant difference in HHF risks between DPP4i and SU use. However, the sensitivity analysis which re-defined the index date as the initiation of a study drug (sensitivity analysis 5) revealed an inconsistent finding; that is, the use of DPP4is versus SUs had a significantly higher HHF risk (Table S2). Also, the analyses of individual DPP4is versus SUs showed that a higher risk of HHF was associated with the use of vildagliptin. Although no CVOTs evaluated the effect of vildagliptin on HHF, an unfavorable effect on ventricular function associated with vildagliptin has been reported in a randomized placebo-controlled trial.[37] Nevertheless, given the limited evidence on HHF risks associated with DPP4is among T2D patients with advanced CKD today, the clinical use of DPP4is should be cautious and the regular monitoring on cardiac function remains essential in clinical practice. Future research is warranted

to explore heterogeneous treatment effects of different DPP4is on clinical outcomes in this population.

Hypoglycemia and all-cause death risks of DPP4is in T2D patients with advanced CKD

In addition to comparable safety profiles on renal and cardiovascular outcomes between DPP4is and SUs, both a lower hospitalized hypoglycemia risk in our study and a lower hypoglycemia risk consistently across all eGFR subgroups in the CAROLINA trial[16] associated DPP4is versus SUs are supporting evidence for the rational use of DPP4is in T2D patients with advanced CKD, who are more vulnerable to hypoglycemic events compared with the general T2D population.[38] The potential benefit of reducing all-cause mortality associated with DPP4is versus SUs was revealed in the primary analysis but not fully confirmed in all sensitivity analyses, which suggests a pivotal topic for further research among this population with a higher mortality risk.

Study strengths and limitations

This study focused on T2D patients with advanced CKD, who have been under-represented in previous clinical trials and real-world studies, to provide additional evidence for supporting rational glucose-lowering treatment in clinical practice. Methodologically, we employed a rigorous study design and analytic procedures to ensure the generalizability and validity of the study results, including 1) the prevalent-user cohort design to include a broader representative of the real-world population treated with DPP4is or SUs for the comprehensive assessment of treatment safety, while the incident-user cohort design as an additional sensitivity analysis to ensure the internal validity of study results, 2) two-step matching procedures to

achieve a greater level of comparability between study groups, 3) competing risk of death modeling approaches to more accurately estimate the risk of disease and event outcomes, and 4) subgroup and sensitivity analyses to examine the robustness of the primary analysis results.

Study limitations should also be acknowledged. First, like other observational studies using administrative claims data, unmeasurable confounding effects (e.g., physician's preferences, laboratory data) might exist. However, efforts to minimize these effects were made through the rigorous matching algorithm to achieve a greater level of between-group comparability on various baseline patient characteristics (e.g., prior GLA exposure history, comorbidities, and complications). Further, due to no information of eGFR level or exact CKD stadium available in our database, the between-group comparability in baseline renal function would be of concern and confounding by indication from imbalanced renal functions may not be ruled out. However, we have implemented several procedures to minimize these concerns, including the use of rigorous enrollment criteria for the national pre-ESRD P4P program to include patients with confirmed CKD stages 3b-5, the exclusion of patients with chronic dialysis or prior ESA use before the index date, and the adjustment for prior metformin exposure in the analyses. Second, medication non-adherence is a challenging issue in real-world studies and may bias study findings. We thus restricted the study cohort to only stable users of DPP4is or SUs to eliminate the potential confounding effect from the short-term use or non-adherence of study drugs. Further, we performed sensitivity analyses based on the as-treated scenario in which patients who discontinued or switched to another drug were censored to corroborate the primary findings under the intention-to-treat scenario. Third, our analyses did not adjust for multiple statistical testing, and therefore, future research that corroborate our findings should consider to apply appropriate adjustments for

multiple testing correction. Fourth, the analyses were stratified by individual DPP4is as the study drugs of interest, but we did not further analyze individual SUs as the comparator drugs for DPP4is which deserves for future research. Finally, the generalizability of our findings may be limited to healthcare systems with universal health insurance coverage.

In summary, among real-world T2D patients with advanced CKD, the use of DPP4is versus SUs was associated with similar safety profiles on renal and cardiovascular outcomes, and reduced risks of hospitalized hypoglycemia and all-cause death. However, the HHF risk may vary across different DPP4is. Future research is encouraged to explore heterogeneous treatment effects of individual DPP4is in a real-world diverse T2D population with various levels of underlying renal and cardiovascular functions to corroborate our study findings.

Study highlights

- What is the current knowledge on the topic?

  The first-line therapeutic options for real-world patients with type 2 diabetes (T2D) and advanced chronic kidney disease (CKD) may be limited to dipeptidyl peptidase-4 inhibitors (DPP4is) and sulfonylureas (SUs) because of the lower tolerability to adverse effects of other glucose-lowering agents in this population.
- What question did this study address?

  What is the comparative renal and cardiovascular safety of DPP4is versus SUs in T2D patients with advanced CKD?
- What does this study add to our knowledge?

  Compared with SUs, DPP4is had no significant difference in the risks of the composite renal outcome, hospitalized heart failure (HHF), major adverse

cardiovascular event (MACE), but reduced risks of hospitalized hypoglycemia and all-cause death among T2D patients with advanced CKD.

- How might this change clinical pharmacology or translational science?

  Considering comparable safety profiles on renal and cardiovascular outcomes as well as benefits of reducing hospitalized hypoglycemia risk and all-cause mortality between DPP4is and SUs, DPP4is may be preferred for patients with T2D and advanced CKD. In clinical practice, the regular monitor on cardiac function remains crucial among this population who are at a higher risk of HHF.

Acknowledgments:

We are grateful to Health Data Science Center, National Cheng Kung University Hospital, for providing administrative and technical support. Technical/expert advice for this project was supported by the MCDTR from the National Institute of Diabetes and Digestive and Kidney Diseases (grant number P30DK092926) (Shihchen Kuo).

Author Contributions:

C.T.Y. and H.T.O. wrote the manuscript; C.T.Y., W.H.L., H.T.O., and S.K. designed the research; C.T.Y., W.H.L., L.J.L., H.T.O., and S.K. performed the research; C.T.Y. and L.J.L. analyzed the data; H.T.O. contributed analytic tools.

References

1. Bailey, R.A., Wang, Y., Zhu, V., Rupnow, M.F. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. *BMC Res. Notes.* 7, 415 (2014).

2. Afkarian, M. et al. Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988-2014. *JAMA.* 316, 602-610 (2016).
3. Jitraknatee, J., Ruengorn, C., Nochaiwong, S. Prevalence and Risk Factors of Chronic Kidney Disease among Type 2 Diabetes Patients: A Cross-Sectional Study in Primary Care Practice. *Sci. Rep.* 10, 6205 (2020).
4. Rodriguez-Poncelas, A. et al. Prevalence of chronic kidney disease in patients with type 2 diabetes in Spain: PERCEDIME2 study. *BMC Nephrol.* 14, 46 (2013).
5. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. *Diabetes Care.* 43(Supplement 1), S98-S110 (2020).
6. Garber, A.J. et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2020 executive summary. *Endocr. Pract.* 26, 107-139 (2020).
7. Shiba, N., Shimokawa, H. Chronic kidney disease and heart failure-Bidirectional close link and common therapeutic goal. *J. Cardiol.* 57, 8-17 (2011).
8. Lo, C. et al. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane Database Syst. Rev.* 9, CD011798 (2018).
9. van Dalem, J. et al. Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: population based cohort study. *BMJ.* 354, i3625 (2016).
10. Scirica, B.M. et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N. Engl. J. Med.* 369, 1317-1326 (2013).
11. White, W.B. et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N. Engl. J. Med.* 369, 1327-1335 (2013).
12. Zannad, F. et al. Heart failure and mortality outcomes in patients with type 2

diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet.* 385, 2067-2076 (2015).
13. Green, J.B. et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N. Engl. J. Med.* 373, 232-242 (2015).
14. Cornel, J.H. et al. Effect of Sitagliptin on Kidney Function and Respective Cardiovascular Outcomes in Type 2 Diabetes: Outcomes From TECOS. *Diabetes Care.* 39, 2304-2310 (2016).
15. Rosenstock, J. et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA.* 321, 69-79 (2019).
16. Rosenstock, J. et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA.* 322, 1155-1166 (2019).
17. Perkovic, V. et al. Effects of Linagliptin on Cardiovascular and Kidney Outcomes in People With Normal and Reduced Kidney Function: Secondary Analysis of the CARMELINA Randomized Trial. *Diabetes Care.* 43, 1803-1812 (2020).
18. Ou, S.M. et al. Effects on Clinical Outcomes of Adding Dipeptidyl Peptidase-4 Inhibitors Versus Sulfonylureas to Metformin Therapy in Patients With Type 2 Diabetes Mellitus. *Ann. Intern. Med.* 163, 663-672 (2015).
19. Ou, H.T., Chang, K.C., Li, C.Y., Wu, J.S. Comparative cardiovascular risks of dipeptidyl peptidase 4 inhibitors with other second- and third-line antidiabetic drugs in patients with type 2 diabetes. *Br. J. Clin. Pharmacol.* 83, 1556–1570 (2017).
20. Filion, K.B. et al. A Multicenter Observational Study of Incretin-based Drugs and Heart Failure. *N. Engl. J. Med.* 374, 1145-1154 (2016).

21. Kim, K.J. et al. Dipeptidyl peptidase-4 inhibitor compared with sulfonylurea in combination with metformin: cardiovascular and renal outcomes in a propensity-matched cohort study. *Cardiovasc. Diabetol.* 18, 28 (2019).
22. Hsieh, C.Y. et al. Taiwan's National Health Insurance Research Database: past and future. *Clin. Epidemiol.* 11, 349-358 (2019).
23. Hsieh, H.M. et al. Economic evaluation of a pre-ESRD pay-for-performance programme in advanced chronic kidney disease patients. *Nephrol. Dial. Transplant.* 32, 1184–1194 (2016).
24. Hung, S.C. et al. Metformin Use and Mortality in Patients With Advanced Chronic Kidney Disease: National, Retrospective, Observational, Cohort Study. *Lancet Diabetes Endocrinol.* 3, 605-614 (2018).
25. Yang, C.T., Yang, C.Y., Ou, H.T., Kuo, S. Comparative cardiovascular safety of GLP-1 receptor agonists versus other glucose-lowering agents in real-world patients with type 2 diabetes: a nationwide population-based cohort study. *Cardiovasc. Diabetol.* 19, 83 (2020).
26. Austin, P.C. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. *Commun. Stat. Simul. Comput.* 38, 1228-1234 (2009).
27. Yang, D., Dalton, J.E. A unified approach to measuring the effect size between two groups using SAS®. SAS Global Forum 2012: Statistics and Data Analysis, Paper 335-2012.
28. Fine, J.P., Gray, R.J. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J. Am. Stat. Assoc.* 94, 496-509 (1999).
29. Austin, P.C., Lee, D.S., Fine, J.P. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation*. 133, 601-609 (2016).
30. Mosenzon, O. et al. Effect of Saxagliptin on Renal Outcomes in the

SAVOR-TIMI 53 Trial. *Diabetes Care.* 40, 69-76 (2017).

31. Xie, Y. et al. Comparative Effectiveness of SGLT2 Inhibitors, GLP-1 Receptor Agonists, DPP-4 Inhibitors, and Sulfonylureas on Risk of Kidney Outcomes: Emulation of a Target Trial Using Health Care Databases. *Diabetes Care.* dc201890 (2020).
32. Huang, T.L., Hsiao, F.Y., Chiang, C.K., Shen, L.J., Huang, C.F. Risk of cardiovascular events associated with dipeptidyl peptidase-4 inhibitors in patients with diabetes with and without chronic kidney disease: A nationwide cohort study. *PLoS One.* 14, e0215248 (2019).
33. Hung, Y.C., Lin, C.C., Huang, W.L., Chang, M.P., Chen, C.C. Sitagliptin and risk of heart failure hospitalization in patients with type 2 diabetes on dialysis: A population-based cohort study. *Sci. Rep.* 6, 30499 (2016).
34. Chan, S.Y., Ou, S.M., Chen, Y.T., Shih, C.J. Effects of DPP-4 inhibitors on cardiovascular outcomes in patients with type 2 diabetes and end-stage renal disease. *Int. J. Cardiol.* 218, 170-175 (2016).
35. Chen, D.Y. et al. Sitagliptin and cardiovascular outcomes in diabetic patients with chronic kidney disease and acute myocardial infarction: A nationwide cohort study. *Int. J. Cardiol.* 181, 200-206 (2015).
36. Liang, C.Y. et al. Cardiovascular risk of sitagliptin in ischemic stroke patients with type 2 diabetes and chronic kidney disease: A nationwide cohort study. *Medicine (Baltimore).* 97, e13844 (2018).
37. McMurray, J.J.V. et al. Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure: A Randomized Placebo-Controlled Trial. *JACC Heart Fail.* 6, 8-17 (2018).
38. Moen, M.F. et al. Frequency of Hypoglycemia and Its Significance in Chronic Kidney Disease. *Clin. J. Am. Soc. Nephrol.* 4, 1121–1127 (2009).

Figure legends

Figure 1: Patient selection flowchart

Abbreviations: T2D, type 2 diabetes; CKD, chronic kidney disease; NHIRD, National Health Insurance Research Database; ESRD, end-stage renal disease; P4P: pay-for-performance; GLAs, glucose-lowering agents; DPP4is, dipeptidyl peptidase-4 inhibitors; SUs, sulfonylureas; ESA, erythropoiesis-stimulating agent.

Notes:

[a]Index date refers to the date of the confirmation of stable use of a study drug (i.e., the third refill of a study drug) after pre-ESRD program enrollment.

[b]Patients who exposed to both DPP4is and SUs in the identification period of study drug users (e.g., the period for the stable use of a study drug being confirmed) were excluded to reduce the misclassification bias.

Figure 2: Association of individual DPP4is versus SUs with study outcomes under intention-to-treat scenario

Abbreviations: DPP4is, dipeptidyl peptidase-4 inhibitors; SUs, sulfonylureas; HHF, hospitalized heart failure; 3P-MACE, three-point major adverse cardiac event; 4P-MACE, four-point major adverse cardiac event.

Notes:

[a]Composite renal outcome included chronic dialysis or kidney transplant.

[b]3P-MACE included non-fatal myocardial infarction, non-fatal stroke, or death due to cardiovascular diseases.

[c]4P-MACE included non-fatal myocardial infarction, non-fatal stroke, hospitalized heart failure, or death due to cardiovascular diseases.

Supplemental Files

1. Table S1
2. Table S2
3. Table S3
4. Figure S1
5. Figure S2

Table 1. Baseline patient characteristics of study cohort before and after matching

Characteristics	Before matching			After matching		
	DPP4is	SUs	Standardized difference[a]	DPP4is	SUs	Standardized difference[a]
Number of subjects	3,988	3,382		1,204	1,204	
GLA utilization pattern in the year prior to the initiation of study drugs						
Number of GLAs prescribed (mean±SD)	2.21±1.31	1.94±1.09	0.22[a]	2.11±1.48	2.04±1.39	0.05
Medication possession ratio (mean±SD)[b]						
Metformin	0.53±0.33	0.60±0.33	-0.23[a]	0.56±0.34	0.49±0.33	0.08
Sulfonylureas	0.45±0.32	0.74±0.30	-1.54[a]	0.52±0.34	0.49±0.35	-0.03
Meglitinides	0.58±0.35	0.42±0.35	0.65[a]	0.45±0.34	0.45±0.35	0.05
Thiazolidinediones	0.50±0.35	0.57±0.34	-0.03	0.45±0.33	0.42±0.33	0.02
Acarbose	0.54±0.34	0.61±0.35	-0.04	0.53±0.36	0.50±0.35	-0.02
DPP4is	0.57±0.34	0.39±0.31	1.06[a]	0.32±0.32	0.43±0.33	0.04
GLP-1RAs	0.36±0.36	0.29±0.27	-0.02	0.15±NA[d]	0.32±0.30	-0.08

Insulins	0.56±0.40	0.37±0.39	0.35[a]	0.40±0.39	0.36±0.38	0.03
Characteristics in propensity score matching						
Age at the initiation of study drugs (years, mean±SD)	66.42±13.02	66.47±12.50	-0.00	66.38±12.78	65.65±12.89	0.06
Male (%)	61.33	63.99	-0.05	62.51	63.09	-0.01
Year of the initiation of study drugs (%)						
2012	24.16	41.78	-0.38[a]	24.62	27.69	-0.07
2013	19.63	20.80	-0.03	23.56	24.62	-0.02
2014	28.77	20.33	0.20[a]	27.37	24.62	0.06
2015	27.44	17.08	0.25[a]	24.45	23.08	0.03
Duration of diabetes (years, mean±SD)	3.40±1.90	3.13±1.78	0.15[a]	3.30±1.92	3.18±1.91	0.06
Metformin exposure within 90 days prior to the initiation of study drugs (%)	17.08	28.09	-0.27[a]	26.77	27.43	-0.01
Diabetes-related complications (%)[c]						
Cardiovascular diseases	34.30	29.89	0.09	33.58	32.09	0.03

Myocardial infarction	3.84	2.66	0.07	3.82	3.66	0.01
Ischemic heart diseases	25.18	22.50	0.06	23.52	23.61	-0.00
Heart failure	15.15	11.32	0.11[a]	14.63	13.63	0.03
Stroke	20.51	19.25	0.03	20.62	20.28	0.01
Retinopathy	26.03	22.21	0.09	23.11	23.61	-0.01
Neuropathy	20.31	19.63	0.02	20.70	20.86	-0.00
Peripheral vascular diseases	9.68	7.92	0.06	9.64	10.06	-0.01
Hypoglycemia	8.45	6.03	0.09	8.40	8.06	0.01
DKA or HHS	2.13	2.13	0.00	2.24	3.33	-0.07
Comorbidities (%)[c]						
Hypertension	84.75	84.48	0.01	85.20	84.95	0.01
Dyslipidemia	49.12	51.01	-0.04	48.46	54.20	-0.11[a]
Cancers	11.13	10.97	0.01	11.55	10.39	0.04
Gastrointestinal diseases	30.24	30.31	-0.00	32.75	31.67	0.02
Musculoskeletal diseases	48.14	50.18	-0.04	49.30	52.04	-0.07

Pulmonary diseases	13.79	11.41	0.07	14.38	12.39	0.06
Mental illnesses	10.53	8.72	0.06	9.73	8.23	0.05
CVD-related medication history (%)[c]						
Lipid-modifying agents	39.47	46.57	-0.14[a]	39.24	43.23	-0.08
Alpha blockers	10.31	12.83	-0.08	10.14	11.55	-0.05
Beta blockers	30.09	36.22	-0.13[a]	32.75	32.34	0.01
RAAS agents	49.12	62.18	-0.27[a]	52.45	55.86	-0.07
Diuretics	30.99	38.47	-0.16[a]	35.25	37.32	-0.04
Calcium channel blockers	37.86	47.75	-0.20[a]	41.73	44.06	-0.05
Antiarrhythmics	2.51	2.63	-0.01	2.41	2.58	-0.01
Cardiac glycosides	2.53	2.28	0.02	2.00	2.00	0.00
Vasodilators	13.11	14.64	-0.04	12.22	13.97	-0.05
Antithrombotics	32.97	41.45	-0.18[a]	35.08	37.66	-0.05
Anticoagulants	1.63	1.89	-0.02	1.66	1.74	-0.01

Abbreviations: DPP4is, dipeptidyl peptidase-4 inhibitors; SUs, sulfonylureas; SMD, standardized mean difference; GLA, glucose-lowering agent; SD, standard deviation; GLP-1RAs, glucagon-like peptide-1 receptor agonists; MPR, medication possession ratio; NA, not available; DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; CVD, cardiovascular disease; RAAS, renin-angiotensin-aldosterone system.

Notes:

[a]An absolute value of standardized difference of higher than or equal to 0.10 indicates a clinical difference between study groups.

[b]The medication possession ratio was calculated as the total day supply of each class of glucose-lowering agents in the year prior to the initiation of study drugs divided by 365 days.

[c]The characteristics were measured in the year prior to or at the initiation of a study drug which refers to the first date of prescription of the study drug after pre-end-stage renal disease (ESRD) pay-for-performance (P4P) enrollment in 2011-2015.

[d]The standard deviation was not available due to limited sample size.

Table 2. Primary analyses for the event rate (/100 person-years) and hazard ratio (95% CI) of study outcomes under intention-to-treat scenario

Study outcomes	**DPP4is (n=1,204)**		**SUs (n=1,204)**		**SDHR**
	Number of events	Event rate (/100 PYs)	Number of events	Event rate (/100 PYs)	**(95% CI)**[d]
Composite renal outcome[a]	278	9.64	245	8.21	1.10 (0.93-1.31)
HHF	225	7.61	205	6.68	1.11 (0.95-1.30)
3P-MACE[b]	144	4.62	148	4.61	0.97 (0.79-1.19)
4P-MACE[c]	298	10.48	295	10.03	1.08 (0.94-1.24)
Hospitalized hypoglycemia	108	3.45	193	6.33	0.53 (0.43-0.64)
All-cause death	108	3.27	153	4.51	0.71 (0.53-0.96)

Abbreviations: DPP4is, dipeptidyl peptidase-4 inhibitors; SUs, sulfonylureas; PYs, person-years; HR, hazard ratio; CI, confidence interval; SDHR, subdistribution hazard ratio; CSHR, cause-specific hazard ratio; HHF, hospitalized heart failure; 3P-MACE, three-point major adverse cardiac event; 4P-MACE, four-point major adverse cardiac event; NA, not applicable.

Notes:

[a]Composite renal outcome included chronic dialysis or kidney transplant.

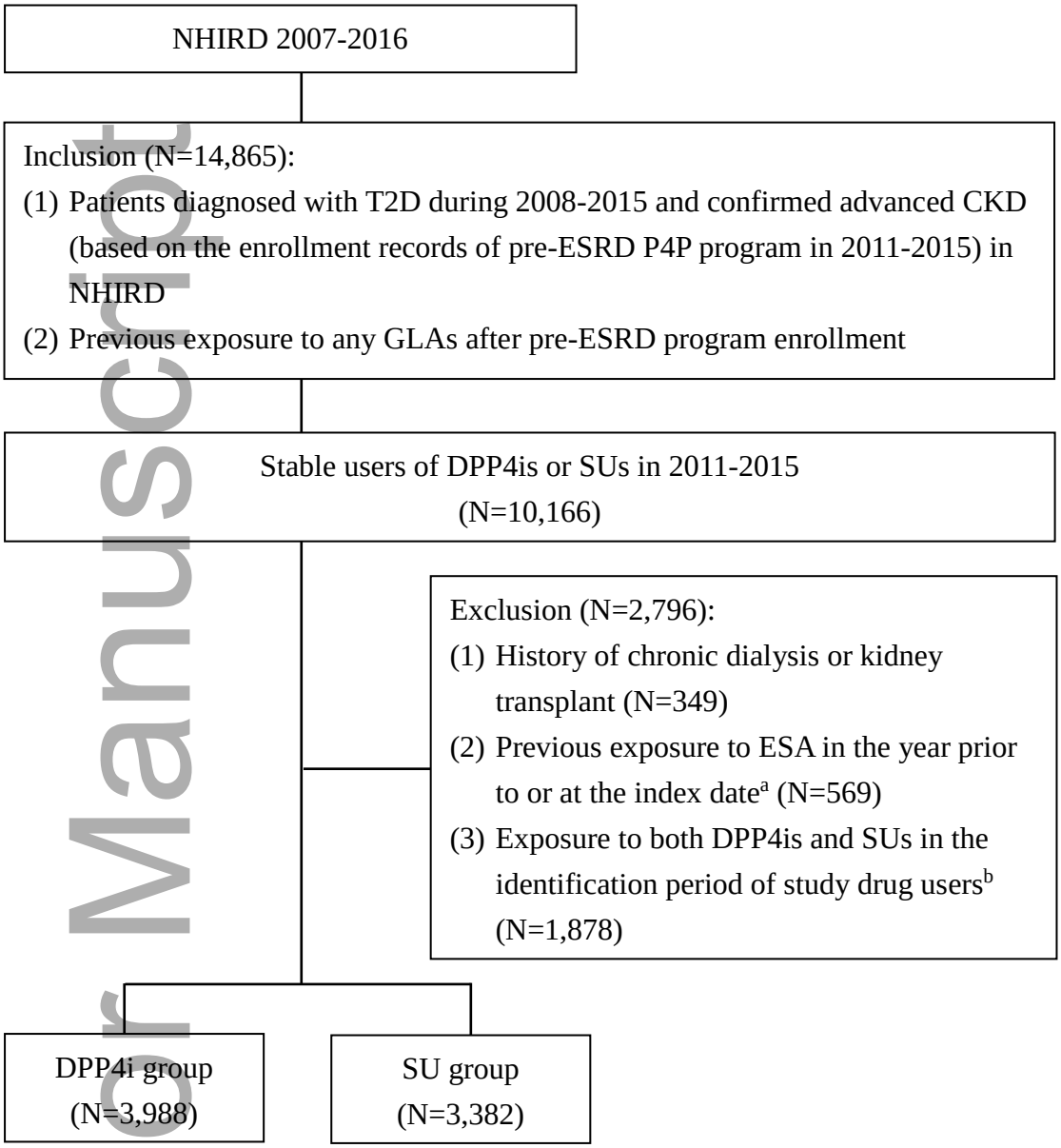
[b]3P-MACE included non-fatal myocardial infarction, non-fatal stroke, or death due to cardiovascular diseases.

[c]4P-MACE included non-fatal myocardial infarction, non-fatal stroke, hospitalized heart failure, or death due to cardiovascular diseases.

[d]The variables adjusted in the hazard models included the history of SU exposure, DPP4i exposure, and dyslipidemia (measured in the year before the initiation of a study drug).

[e]The relative hazard of all-cause death of DPP4is compared with SUs was estimated using Cox models instead of subdistributional hazard models.

Figure 1. Patient selection flowchart

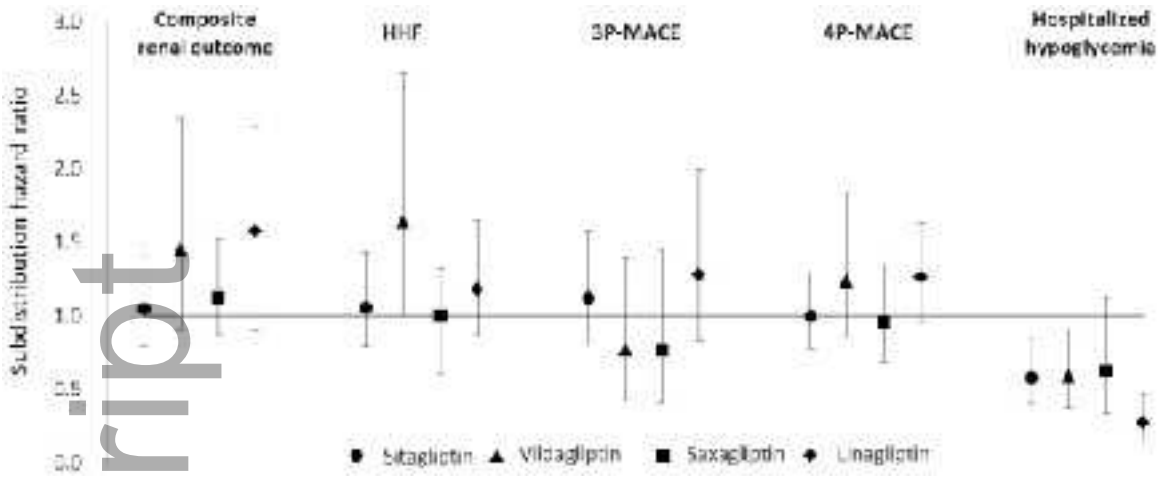


Abbreviations: T2D, type 2 diabetes; CKD, chronic kidney disease; NHIRD, National Health Insurance Research Database; ESRD, end-stage renal disease; P4P: pay-for-performance; GLAs, glucose-lowering agents; DPP4is, dipeptidyl peptidase-4 inhibitors; SUs, sulfonylureas; ESA, erythropoiesis-stimulating agent.

Notes:

[a]Index date refers to the date of the confirmation of stable use of a study drug (i.e., the third refill of a study drug) after pre-ESRD program enrollment.

[b]Patients who exposed to both DPP4is and SUs in the identification period of study drug users (e.g., the period for the stable use of a study drug being confirmed) were excluded to reduce the misclassification bias.



cpt_2262_f2.jpg