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Effects of intensifying triple oral antidiabetic drug therapy by initiating insulin versus enhancing oral antidiabetic drug therapy on clinical outcomes in patients with type 2 diabetes: a nationwide population-based, propensity score-matched cohort study

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Abstract

Aims:

In real-world clinical practice, insulin is commonly initiated later in the antidiabetic treatment course, but information is lacking on diabetes complications associated with initiating insulin as the fourth-line antidiabetic therapy versus enhancing oral antidiabetic drug (OAD) therapy in type 2 diabetes mellitus (T2DM) patients with triple OAD therapy failure.

Materials and Methods:

We conducted a nationwide population-based, retrospective cohort study involving 1,022 (without prevalent diabetes-related complications [PDRCs]) and 2,077 (with/without PDRCs) propensity score-matched pairs of fourth-line insulin therapy users and enhanced OAD therapy users identified in 2004-2010. Clinical outcomes including the composite cardiovascular outcome (myocardial infarction, stroke, heart failure [HF], or ischemic heart diseases [IHDs]), peripheral vascular diseases (PVDs), hypoglycemia, and all-cause mortality were assessed through 2013. Hypoglycemia was adjusted in Cox models to consider its potential effect on study outcomes.

Results:

In a T2DM cohort without PDRCs, fourth-line insulin therapy was not associated with increased risks of clinical outcomes, except hypoglycemia (hazard ratio [HR], 1.45; 95% CI, 1.02-2.07), compared with enhanced OAD therapy. Among T2DM patients with/without PDRCs, fourth-line insulin therapy was associated with increased risks of the composite cardiovascular outcome (1.23; 1.03-1.46), HF (1.59; 1.12-2.25), IHDs (1.37; 1.09-1.73), PVDs (1.17; 1.00-1.36), hypoglycemia (1.49; 1.20-1.85), and all-cause mortality (1.48; 1.01-2.17), but adjustment for hypoglycemia significantly attenuated the risks of HF (1.34; 0.92-1.94), PVDs (1.15; 0.98-1.34), and all-cause mortality (1.30; 0.84-1.99).

Conclusions:

Initiation of fourth-line insulin therapy can be considered for T2DM patients with triple OAD therapy failure, and the importance of awareness and prevention of hypoglycemia among insulin-treated T2DM patients cannot be overstated.

Introduction

Early insulin initiation is suggested to preserve ² -cell function,[1-3] but in real-world clinical practice insulin is still commonly prescribed in a later stage of an antidiabetic treatment course because of clinical inertia.[4] Most patients with type 2 diabetes mellitus (T2DM) generally do not begin insulin therapy until they have experienced poor glycemic control using three oral antidiabetic drugs (OADs).[5] Patients often get delayed insulin initiation or have poor adherence to insulin therapy because of their fears about difficulty with injections, weight gain, and hypoglycemia.[6-8] Clinicians may have concerns about the safety profile and unfavorable clinical outcomes of insulin, and thus they choose to either maximize doses of three OADs or add another OAD as enhanced OAD therapy for patients with triple OAD therapy failure regardless of the clear recommendation by the American Diabetes Association (ADA)[9] to initiate insulin therapy for these patients.

Current evidence from randomized controlled trials (RCTs) and longitudinal cohort studies about cardiovascular outcomes of insulin therapy in T2DM patients appears controversial. Favorable cardiovascular outcomes of intensive glycemic control using sulfonylureas or insulin versus conventional therapy using diet control were documented in the 10-year follow-up UK Prospective Diabetes Study.[10] However, other RCTs either showed no significant benefits of insulin therapy on cardiovascular outcomes[11,12] or revealed a link between insulin-based therapy and increased non-fatal cardiovascular events.[13] Recently, two meta-analyses of RCTs suggested a neutral effect of insulin therapy on cardiovascular outcomes.[14,15] However, interpretations from these study findings require caution because they had a limited number of cardiovascular events and shorter follow-up periods, sulfonylureas used in these studies[10,12] might also have detrimental effects on cardiovascular diseases (CVDs),[16] and their study populations were specific to either patients at early stage of diabetes[11] or those with existing CVDs.[12,13] On the other hand, longitudinal cohort studies demonstrated an association for T2DM patients between insulin therapy and increased risks of CVDs and all-cause mortality, but effects of insulin therapy were only assessed in patients at an earlier stage of the antidiabetic treatment course, with insulin being used as the monotherapy, second-line, or third-line antidiabetic treatment.[17-24]

Because T2DM is a progressive disease, most patients with T2DM eventually need insulin therapy. Although it is quite common in real-world clinical practice that insulin therapy is initiated in a later stage of an antidiabetic treatment course, effects of insulin used as the fourth-line

antidiabetic treatment in T2DM patients with triple OAD therapy failure remain unknown. Therefore, we first investigated risks of clinical outcomes associated with intensifying triple OAD therapy by initiating insulin (i.e., fourth-line insulin users) versus enhancing OAD therapy (i.e., potential insulin use candidates [PICs]). Second, we sought to determine whether hypoglycemia played a role in the relationship between insulin use and clinical outcomes. Hypoglycemia has been shown to contribute to the risk of developing CVDs,[25-27] and thus we hypothesized that increased hypoglycemia associated with insulin therapy might negatively impact the association between insulin therapy and clinical outcomes. Third, since basal insulin alone is recommended as the initial insulin regimen by the ADA,[9] we performed subgroup analyses to investigate whether effects of insulin therapy differed by insulin regimen.

Materials and Methods

This study was conducted with permission from the Institutional Review Board of National Cheng Kung University Hospital (B-EX-103-015).

Data source:

This was a retrospective cohort study utilizing the Longitudinal Cohort of Diabetes Patients (LHDB) dataset in 1996-2013 from Taiwan's National Health Insurance Research Database (NHIRD) that was released by Taiwan's National Health Research Institutes (NHRI). The NHIRD is population-based and derived from claims data of the National Health Insurance (NHI) program, a mandatory-enrollment, single-payment system that covers over 99% of Taiwan's population.[28] The LHDB is a national representative dataset for the population of diabetic patients in Taiwan and has been validated by Taiwan's NHRI for research purposes.[29] This dataset consists of longitudinal data (e.g., disease diagnosis and prescription utilization records) from a random sample of 120,000 de-identified incident diabetes cases from each calendar year since 1999, who were tracked back to 1996 and followed up to 2013.

Study population:

Study patients extracted from the LHDB were newly diagnosed with T2DM (ICD-9 codes: 250.x0, 250.x2, x=0-9) during 1999-2010. We excluded those under 18 years of age, diagnosed with type 1 diabetes, or gestational diabetes. Selection of the study cohort is detailed in the Supplementary Figure 1.

Exposure to antidiabetic drugs:

The World Health Organization Anatomical Therapeutic Chemical Classification System was used to define antidiabetic drugs in the LHDB. The LHDB in 2004-2010 were used to identify the treatment exposure of interest. Identification of the study cohort started in year 2004 because long-acting insulin analogs (LAIAs) were reimbursed by the NHI program since 2004, and it ended in year 2010 to allow for a follow-up period of at least 3 years (i.e., 2011-2013). During 2004-2010, the index date for the fourth-line insulin group was defined as the first date of initiating fourth-line insulin prescription for triple OAD therapy regimens, and the index date for the PIC group was the first date of enhancing OAD therapy by either increasing three OADs up to maximal doses or adding a fourth-line OAD. Before index date, all patients in two study groups were on sub-maximal doses of at least one of three OADs. Type of insulin was confirmed by labels and drug licensure codes (Supplementary Table 1). Maximal doses of OADs were defined according to information provided by drug product labels (Supplementary Table 2).

Definition of clinical outcomes:

Primary outcomes included a composite outcome of non-fatal/fatal CVDs (i.e., myocardial infarction [MI], cerebrovascular diseases, heart failure, or ischemic heart diseases) and all-cause mortality. Secondary outcomes included individual CVD events, peripheral vascular diseases (PVDs), and hypoglycemia. Using the ICD-9-CM codes, events of hospitalization for CVDs and PVDs were identified from the inpatient claims files, and events of hypoglycemia were identified from the emergency department, inpatient, and outpatient claims files (Supplementary Table 3). The accuracy of disease diagnoses based on ICD-9-CM coding in the NHIRD has been validated in previous studies.[30-35] For example, the positive predictive value for the diagnosis of myocardial infarction, ischemic stroke, and heart failure has been reported to be as high as 93%, 94%, and 98%, respectively. In addition, hypoglycemic events were ascertained according to the validated definition (i.e., having any of the following ICD-9-CM codes: 251.0, 251.1, 251.2, 250.3, 250.8, or 962.3).[36,37] The operational definitions for confirming mortality status have been also validated and described in previous studies.[38,39]

Statistical analyses:

Primary analyses using baseline complication-free patients were conducted on an intention-to-treat (ITT) scenario, where the follow-up for patients started from index date until death, dropout or lost to follow-up from the NHI program, occurrence of study outcomes, or the end of 2013, whichever came first. Considering confounding by indication and selection bias,

one-to-one 5-digit greedy propensity score matching (PSM)[40,41] was used to adjust for imbalanced patient characteristics between study groups, in which treatment status was a dependent variable and a comprehensive list of independent variables (Table 1 and Supplementary Table 4)[37,42] were selected a priori based on clinical importance related to selection of antidiabetic drug regimens and study outcomes. The variables used for the PSM included demographics, comorbidities, diabetes-related complications, antidiabetic drugs, CVD-related medications, and so on. Standardized mean difference (SMD) was used to test the difference in patient characteristics between study groups, and the absolute value of SMD larger than 0.1 indicated statistically significant imbalance of patient characteristics between study groups.[43-45]

Incidence rate of study outcomes was calculated as the total number of events over the follow-up period divided by person-years at risk. Cox proportional hazards models were used to compare risks of study outcomes between two PS-matched cohorts. Hazard ratios (HRs) and two-tailed 95% confidence intervals (CIs) were computed. A two-tailed p value of <0.05 was considered statistically significant. Cumulative sums of martingale-based residuals were used to check the proportional hazard assumption in Cox models.[46] To consider the potential effect of hypoglycemia on study outcomes, we adjusted for the presence of hypoglycemia after index date as a covariate in Cox models. Before adjustment for hypoglycemia, we assessed the total effect of the fourth-line insulin therapy versus the enhanced OAD therapy on risks of CVDs and death, while after adjustment for hypoglycemia, we assessed the remaining effect of the fourth-line insulin therapy after the partial effect of hypoglycemia was considered. Akaike's information criterion (AIC) was used to evaluate the quality of model fit between models with and without adjustment for hypoglycemia; a model with a lower AIC has better fit.

Secondary analyses were conducted in a larger cohort incorporating the study cohort for primary analyses with those patients having prevalent diabetes-related complications (PDRCs) at baseline (one year before index date). The history of PRDCs was additionally considered in the PSM procedure. This analysis was conducted with the consideration that some T2DM patients may have already had comorbid diseases before initiating insulin, and thus the secondary analysis results could be generalizable to the T2DM population in real-world clinical practice.

Sensitivity and subgroup analyses were performed using the study cohort for primary analyses. First, as-treated scenario analysis was conducted to account for over-estimation of the treatment effect from primary analyses, where non-adherence to medications was ignored. In addition to the

censored definitions in primary analyses, patients were also censored when medication treatment patterns changed. Second, we re-defined maximal doses of OADs according to clinicians' discretion/recommendations (Supplementary Table 2) in selecting the PIC group to account for the real-world clinical practice variation in using maximal doses of OADs. Third, we refined the definitions for stable users of fourth-line insulin or enhanced OAD therapy by adding another criterion that fourth-line insulin or enhanced OAD therapy needed to last for at least 180 days after index date. Fourth, compared with enhanced OAD therapy, subgroup analyses were conducted to evaluate the effects of different fourth-line insulin initiation regimens, including basal insulin (i.e., intermediate-acting human insulin [IAHI] or LAIAs) alone and LAIAs alone. SAS software (version 9.4) was utilized for all analyses.

Results

Study cohort characteristics:

We identified 3,959 complication-free patients, with 1,186 in the fourth-line insulin group and 2,773 in the PIC group (Supplementary Figure 1). Table 1 shows patient characteristics by study group. After PSM, we included 1,022 patients in each group for primary analyses; there was no statistical difference in patient characteristics between treatment groups. Supplementary Table 5 provides follow-up time for each study outcome in primary analyses.

Primary analyses:

The HR (95% CI) of fourth-line insulin users versus PICs was 1.37 (0.99-1.89) and 1.53 (0.80-2.94) for the composite outcome of CVDs and all-cause death, respectively (Table 2). The HR (95% CI) for individual CVD events ranged from 0.67 (0.27-1.63) for MI to 1.64 (0.77-3.46) for heart failure. The HR (95% CI) was 1.20 (0.91-1.58) and 1.45 (1.02-2.07) for PVDs and hypoglycemia, respectively. Adjustment for hypoglycemia significantly reduced HRs for most study outcomes, e.g., HR decreased by 20%, from 1.53 to 1.23, for all-cause death. Hypoglycemia-adjusted Cox models yielded lower AIC values for all study outcomes. Supplementary Table 6 shows that the fourth-line insulin group had a higher proportion of experiencing hypoglycemia.

Secondary analyses:

In secondary analyses, we identified 2,077 T2DM patients with or without PDRCs in each group after PSM; there was no statistical difference in patient characteristics between groups

(Supplementary Table 4). The HR (95% CI) of fourth-line insulin users versus PICs was significantly increased for the composite outcome of CVDs (1.23; 1.03-1.46), heart failure (1.59; 1.12-2.25), ischemic heart diseases (1.37; 1.09-1.73), PVDs (1.17; 1.00-1.36), hypoglycemia (1.49; 1.20-1.85), and all-cause death (1.48; 1.01-2.17). Likewise, hypoglycemia-adjustment significantly reduced the HRs and yielded lower AIC values for study outcomes. It is worth noting that the hypoglycemia-adjusted HRs (95% CI) were no longer statistically significant for heart failure (1.34; 0.92-1.94), PVDs (1.15; 0.98-1.34), and all-cause death (1.30; 0.84-1.99) (Supplementary Table 7).

Sensitivity and subgroup analyses:

Results of sensitivity analyses (Supplementary Tables 8-10) were consistent with those in primary analyses. In subgroup analyses, we selected two subgroups from the fourth-line insulin group, including (1) 598 patients who initiated basal insulin alone vs. 598 PS-matched PIC patients and (2) 517 patients who initiated LAIAs alone vs. 517 PS-matched PIC patients. The group of patients initiating LAIAs alone was a subgroup of patients initiating basal insulin alone. As shown in Table 3 and Supplementary Tables 11 and 12, HRs for each study outcome were not statistically significant, except for hypoglycemia (1.45) in primary analyses, when comparing the entire fourth-line insulin group with the PS-matched PIC group. Of note, however, there was an obvious decreased trend in HRs for the composite outcome of CVDs, MI + cerebrovascular diseases, and PVDs for patients initiating any types of insulin, patients initiating basal insulin alone, and patients initiating LAIAs alone compared with their PS-matched PIC group patients; for example, the HR for the composite outcome of CVDs decreased from 1.37 to 1.00 and to 0.89.

Discussion

The ADA explicitly recommends insulin therapy for T2DM patients with triple therapy failure.[9] In current clinical practice, however, a high proportion of such patients is still treated with either increasing doses of three OADs or adding another OAD instead of initiating fourth-line insulin therapy. To our knowledge, this is the first large nationwide cohort study that evaluated the effects of initiating fourth-line insulin therapy in a real-world setting. First, we found that, in a T2DM cohort without PDRCs, initiating fourth-line insulin versus enhancing OAD therapy was not associated with increased risks of CVDs, PVDs, and all-cause mortality. Second, in a T2DM population with or without PDRCs, fourth-line insulin was associated with increased risks of the composite outcome of CVDs, heart failure, ischemic heart diseases, PVDs, and all-cause mortality.

Third, fourth-line insulin was associated with a higher risk of hypoglycemia than enhanced OAD therapy. Adjusting for hypoglycemia reduced the risks of study outcomes and yielded lower AIC values of models, suggesting that hypoglycemia had a significant effect in the association between insulin therapy and increased CVDs and all-cause mortality risks. Noteworthily, among the T2DM population with or without PDRCs, adjusting for hypoglycemia would neutralize excess risks of heart failure, PVDs, and all-cause mortality, which emphasizes the importance of awareness and prevention of hypoglycemia among insulin-treated T2DM patients. Fourth, compared with their own PS-matched PIC groups, initiation of fourth-line insulin therapy using LAIAs alone was associated with a lower risk of the composite outcome of CVDs, MI + cerebrovascular diseases, and PVDs.

Effects of the fourth-line insulin versus enhanced OAD therapy on clinical outcomes:

Association of insulin therapy with incident CVDs and mortality has been investigated previously, but evidence is lacking on the effects of initiating insulin as the fourth-line antidiabetic treatment in T2DM patients. Previous longitudinal studies evaluated the effects of insulin therapy when it was used as monotherapy,[17,24] second-line,[17-21,24] or third-line[22-24] treatment, and revealed a harmful effect of insulin therapy on CVDs and all-cause mortality. Unlike previous studies, we found that intensification of triple OAD therapy by initiating fourth-line insulin versus enhancing OAD therapy was not associated with increased risks of the composite or individual outcomes of CVDs, PVDs, and all-cause mortality in the complication-free T2DM patients, although it was associated with increased risks of some clinical outcomes among patients with or without PDRCs. Noteworthily, one major concern in the previous studies is the bias due to confounding by indication because they compared insulin therapy with non-treatment,[24] or metformin[17,24] or SU[17] as monotherapy, or metformin+SU[18,20,21] or metformin+DPP4i[19] as dual therapy. Indeed, characteristics of insulin users are typically different from patients without any treatments[24] or those with only one or two OADs.[17-19,24] Unlike previous studies, we carefully identified a comparable group to the insulin-treated group and focused on evaluating the effects of fourth-line insulin therapy in T2DM patients with triple OAD therapy failure; in other words, all of our study patients have been candidates for insulin therapy. Moreover, we applied rigorous PSM approaches and identified baseline complication-free patients for primary analyses, which led to more comparable groups, minimized confounding by indication, and therefore ensured causal inference in our study.

Role of hypoglycemia in relationship between insulin therapy and clinical outcomes:

Hypoglycemia is a major undesired effect of insulin therapy, and it may play a role in a causal pathway between insulin therapy and risks of CVDs and mortality. There is supporting evidence linking hypoglycemia with increased risks of CVDs and mortality in patients with T2DM or pre-diabetes,[47-51] but a study reported no significant relationship between severe/symptomatic hypoglycemic events and CVD-specific/all-cause mortality in patients with T2DM starting insulin therapy.[52] Our study found that increased risks of clinical outcomes associated with insulin therapy became less or even vanished after hypoglycemia was adjusted in the analyses, which provides the supporting evidence for the potential effect of hypoglycemia on risks of CVDs and mortality and indicates the use of insulin per se may not be associated with increased risks of CVDs and mortality (Table 2 and Supplementary Table 7). Considering all possible efforts will be made to minimize or avoid hypoglycemia, such findings should reassure health professionals who may be reluctant to start insulin therapy because of the perception that it will have negative impacts on risks of CVDs and mortality.

Effects of initiating different types of insulin versus non-insulin therapy on clinical outcomes:

Basal insulins, especially LAIAs, lead to a lower risk of hypoglycemia than other types of insulin.[53,54] Considering that hypoglycemia may contribute to CVD risks, it would be worth further assessing the effects of LAIAs versus other types of insulin or non-insulin therapy in T2DM. However, there is limited data on this topic. The ORIGIN trial[11] showed that glargine compared with non-insulin therapy had a neutral effect on cardiovascular outcomes. Another study using Swedish national registries[19] demonstrated that second-line treatment using LAIAs versus DPP-4i had a neutral effect on fatal/non-fatal CVDs and all-cause death, and that compared with individual PS-matched DPP4i users, LAIAs had a neutral effect on fatal/non-fatal CVDs and all-cause death, but short-acting insulin, pre-mixed insulin, and IAHI had increased risks. Our subgroup analyses added supporting evidence to the literature - these results might justify the suggestion of first considering LAIAs alone for T2DM patients as the initial insulin therapy regimen.

Strengths and limitations:

There are several advantages of this study. First, this is a study based on a national representative cohort of T2DM patients with a long-term follow-up, and results could be applicable to patients who initiated insulin as the fourth-line antidiabetic treatment, which is a common prescription pattern of insulin use in real-world clinical practice,[4] is a highly recommended

treatment strategy by the ADA for patients with triple OAD therapy failure,[9] and is suggested by Taiwan's NHI program (because insulin is generally more expensive than OADs). Second, rigorous statistical approaches were used to minimize common potential biases, including confounding by indication, selection bias, and immortal-time bias, to ensure causal inference. Third, a series of sensitivity and subgroup analyses were conducted to ensure the robustness of study findings. Particularly, we further broke down different types of insulin to analyze the effects of using LAIAs, which may fill a research gap in previous studies.

Several limitations, however, should be acknowledged. First, we used the PSM to control for patient characteristics between study groups, but like any study using administrative claims data, the residual effects due to unmeasured confounders could not be avoided. The selection bias may occur when the choice of initiating fourth-line insulin or enhancing OAD therapy was made from the decisions of physician-patient discussions. Moreover, data on indicators of diabetes management, such as HbA1c, blood pressure, or lipids, were unavailable in Taiwan's NHIRD. However, the duration and severity of T2DM, the use of OADs regimens and CVD-related medications, and the status of medical comorbidities were similar between study groups at baseline in our cohort study. Although a prospective RCT can overcome the potential confounding by measured or unmeasured covariates, the initiation of a RCT to evaluate the fourth-line antidiabetic treatment options may be less motivated. Second, we targeted insulin use as a fourth-line antidiabetic treatment, which would make our results unsuitable for explaining the effects of insulin initiation as monotherapy, second-line, or third-line treatment. Third, the generalizability of our study findings may be limited to countries with universal health insurance. Lastly, the glucagon-like peptide 1 receptor agonist (liraglutide) and sodium-glucose cotransporter 2 inhibitor (empagliflozin) were not available in Taiwan's NHI program until October 1st, 2012 and May 1st, 2016, respectively, and thus our analyses did not possess sufficient power to assess the effects of these drugs on study outcomes due to very few patients (<0.01%) prescribed with these drugs.

In summary, our findings have important therapeutic implications, supporting the current clinical recommendations to initiate insulin therapy for T2DM patients with triple OAD therapy failure and to provide comprehensive education on avoiding and treating hypoglycemia in any insulin-treated patients. Future prospective trials are warranted to confirm our findings, especially for potential benefits of using LAIAs in T2DM on CVDs and mortality.

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Conflicts of Interest

None reported.

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References:

1. Lingvay I, Kaloyanova PF, Adams-Huet B, Salinas K, Raskin P. Insulin as Initial Therapy in Type 2 Diabetes. J Investig Med. 2007;55(2):62-68.
2. Harrison LB, Adams-Huet B, Raskin P, Lingvay I. ² -cell function preservation after 3.5 years of intensive diabetes therapy. Diabetes Care. 2012;35(7):1406-1412.
3. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on ² -cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet. 2008;371(9626):1753-1760.
4. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes. Diabetes Care. 2013;36(11):3411-3417.
5. Lin SD, Tsai ST, Tu ST, et al. Glycosylated hemoglobin level and number of oral antidiabetic drugs predict whether or not glycemic target is achieved in insulin-requiring type 2 diabetes. Prim Care Diabetes. 2015;9(2):135-141.
6. Peyrot M, Rubin RR, Khunti K. Addressing barriers to initiation of insulin in patients with type 2 diabetes. Primary Care Diabetes. 2010;4:S11-S18.
7. Karter AJ, Subramanian U, Saha C, et al. Barriers to insulin initiation: the translating research into action for diabetes insulin starts project. Diabetes Care. 2010;33(4):733-735.
8. Wen Chen K, Tseng H-M. The Barriers to Initiating Insulin Therapy among People with Type 2 Diabetes in Taiwan - A Qualitative Study. Journal of Diabetes & Metabolism. 2012;03(05).
9. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care. 2017;40(Suppl 1):S64-S74.
10. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. N Engl J Med. 2008;359:1577-1589.
11. ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;2012(367):319-328.
12. Chaitman BR, Hardison RM, Adler D, et al. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease. Circulation. 2009;120(25):2529-2540.
13. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L, DIGAMI 2 Investigators. Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the Diabetes Mellitus

Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. Diabetologia. 2011;54(6):1308-1317.

14. Anyanwagu U, Mamza J, Donnelly R, Idris I. Comparison of cardiovascular and metabolic outcomes in people with type 2 diabetes on insulin versus non-insulin glucose-lowering therapies (GLTs): A systematic review and meta-analysis of clinical trials. Diabetes Res Clin Pract. 2016;121:69-85.
15. Palmer SC, Mavridis D, Nicolucci A, et al. Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes: A Meta-analysis. JAMA. 2016;316(3):313-324.
16. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes, Obesity and Metabolism. 2013;15(10):938-953.
17. Currie CJ, Poole CD, Evans M, Peters JR, Morgan CL. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. J Clin Endocrinol Metab. 2013;98(2):668-677.
18. Roumie CL, Greevy RA, Grijalva CG, et al. Association between intensification of metformin treatment with insulin vs sulfonylureas and cardiovascular events and all-cause mortality among patients with diabetes. JAMA. 2014;311(22):2288-2296.
19. Nystrom T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Second line initiation of insulin compared with DPP-4 inhibitors after metformin monotherapy is associated with increased risk of all-cause mortality, cardiovascular events, and severe hypoglycemia. Diabetes Res Clin Pract. 2017;123:199-208.
20. Ekstrom N, Svensson AM, Miftaraj M, et al. Cardiovascular safety of glucose-lowering agents as add-on medication to metformin treatment in type 2 diabetes: report from the Swedish National Diabetes Register. Diabetes Obes Metab. 2016;18(10):990-998.
21. Gamble JM, Thomas JM, Twells LK, Midodzi WK, Majumdar SR. Comparative effectiveness of incretin-based therapies and the risk of death and cardiovascular events in 38,233 metformin monotherapy users. Medicine (Baltimore). 2016;95(26):e3995.
22. Anyanwagu U, Mamza J, Mehta R, Donnelly R, Idris I. Cardiovascular events and all-cause mortality with insulin versus glucagon-like peptide-1 analogue in type 2 diabetes. Heart. 2016;102(19):1581-1587.
23. Jil M, Rajnikant M, Richard D, Iskandar I. The effects of dual-therapy intensification with

insulin or dipeptidylpeptidase-4 inhibitor on cardiovascular events and all-cause mortality in patients with type 2 diabetes: A retrospective cohort study. Diab Vasc Dis Res. 2017;14(4):295-303.

24. Hippisley-Cox J, Coupland C. Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: cohort study in primary care. BMJ. 2016;354:i3477.
25. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ. 2013;347:f4533.
26. Cha SA, Yun JS, Lim TS, et al. Severe hypoglycemia and cardiovascular or all-cause mortality in patients with type 2 diabetes. Diabetes Metab J. 2016;40(3):202-210.
27. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med. 2010;363:1410-1418.
28. Cheng T-M. Taiwan's new national health insurance program: genesis and experience so far. Health Affairs. 2003;22(3):61-76.
29. Lin CC, Lai MS, Syu CY, Chang SC, Tseng FY. Accuracy of diabetes diagnosis in health insurance claims data in Taiwan. J Formos Med Assoc. 2005;104 (3):157-163.
30. Cheng CL, Kao YH, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf. 2011;20:236-242.
31. Cheng CL, Lee CH, Chen PS, et al. Validation of acute myocardial infarction cases in the National Health Insurance Research database in Taiwan. J Epidemiol. 2014;24:500-507.
32. Chang CH, Lee YC, Tsai CT, et al. Continuation of statin therapy and a decreased risk of atrial fibrillation/flutter in patients with and without chronic kidney disease. Atherosclerosis. 2014;232(1):224-230.
33. Lin YS, Chen TH, Chi CC, et al. Different implications of heart failure, ischemic stroke, and mortality between nonvalvular atrial fibrillation and atrial flutter: a view from a national cohort study. J Am Heart Assoc. 2017;6(7):e006406.
34. Wu CS, Lai MS, Gau SS,Wang SC, Tsai HJ. Concordance between patient self-reports and claims data on clinical diagnoses, medication use, and health system utilization in Taiwan. PLoS One. 2014;9(12):e112257.
35. Sung SF, Hsieh CY, Lin HJ, Chen YW, Yang YH, Li CY. Validation of algorithms to identify stroke risk factors in patients with acute ischemic stroke, transient ischemic attack, or

intracerebral hemorrhage in an administrative claims database. Int J Cardiol. 2016;215:277-282.
36. Ginde AA, Blanc PG, Lieberman RM, Camargo CA Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. BMC Endocr Disord. 2008;8:4.
37. Chang HY, Weiner J, Richards TM, Bleich SN, Segal JB. Validating the adapted Diabetes Complications Severity Index in claims data. Am J Manag Care. 2012;18(11):721-726.
38. Cheng C-L, Chien H-C, Lee C-H, Lin S-J, Yang Y-HK. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in National Health Insurance Research Database in Taiwan. Int J Cardiol. 2015;201:96-101.
39. Ou HT, Chang KC, Li CY, Wu JS. 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. 2017;83(7):1556-1570.
40. Dehejia RH, Wahba S. Propensity score-matching methods for nonexperimental causal studies. Rev Econ Stat. 2002;84(1):151-161.
41. Parsons LS. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference, Cary, NC: SAS Institute Inc., 2001;214-26.
42. Meduru P, Helmer D, Rajan M, Tseng C-L, Pogach L, Sambamoorthi U. Chronic illness with complexity: implications for performance measurement of optimal glycemic control. J Gen Intern Med. 2007;22(3):408-418.
43. Cohen J. Statistical Power Analysis for the Behavioral Sciences (2nd ed). Hillsdale, NJ: Lawrence Erlbaum Associates Publishers; 1988.
44. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput. 2009;38(6):1228-1234.
45. Yang D, Dalton JE. A unified approach to measuring the effect size between two groups using SAS. SAS Global Forum 2012: Statistics and Data Analysis, Paper 335-2012.
46. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80(3):557-572.
47. Lee AK, Warren B, Lee CJ, et al. The Association of Severe Hypoglycemia With Incident Cardiovascular Events and Mortality in Adults With Type 2 Diabetes. Diabetes Care. 2018;41(1):104-111.

48. Goto A, Goto M, Terauchi Y, Yamaguchi N, Noda M. Association Between Severe Hypoglycemia and Cardiovascular Disease Risk in Japanese Patients With Type 2 Diabetes. J Am Heart Assoc. 2016;5(3):e002875.
49. Standl E, Stevens SR, Armstrong PW, et al. Increased Risk of Severe Hypoglycemic Events Before and After Cardiovascular Outcomes in TECOS Suggests an At-Risk Type 2 Diabetes Frail Patient Phenotype. Diabetes Care. 2018;41(3):596-603.
50. Mellbin LG, Rydén L, Riddle MC, et al; ORIGIN Trial Investigators. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J. 2013;34(40):3137-3144.
51. Zinman B, Marso SP, Christiansen E, Calanna S, Rasmussen S, Buse JB; LEADER Publication Committee on behalf of the LEADER Trial Investigators. Hypoglycemia, cardiovascular outcomes, and death: The LEADER Experience. Diabetes Care. 2018;41(8):1783-1791.
52. Freemantle N, Danchin N, Calvi-Gries F, Vincent M, Home P. Relationship of glycaemic control and hypoglycaemic episodes to 4-year cardiovascular outcomes in people with type 2 diabetes starting insulin. Diabetes, Obesity and Metabolism. 2016;18(2):152-158.
53. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. Diabetes Res Clin Pract. 2008;81(2):184-189.
54. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev. 2007(2):CD005613.

Table 1: Patient characteristics of fourth-line insulin users (fourth-line insulin) and potential insulin use candidates (PICs) before and after propensity score matching (primary analysis: complication-free study cohort[1])

Baseline characteristics	Before propensity score matching			After propensity score matching		
	Fourth-line insulin, n = 1,186	PICs, n = 2,773	SMD[2]	Fourth-line insulin, n = 1,022	PICs, n = 1,022	SMD[2]
Age (years) (mean ± SD)	50.97 ± 11.67	53.22 ± 10.73	-0.20	51.51 ± 11.65	51.46 ± 10.42	0.00
Female (%)	39.04	41.90	-0.06	39.24	39.14	0.00
Year of index date[3] (%)						
2004	4.38	6.35	-0.09	4.79	5.48	-0.03
2005	6.66	5.12	0.07	6.26	5.97	0.01
2006	9.27	10.31	-0.03	10.37	9.00	0.05
2007	18.47	11.86	0.18	15.26	15.56	-0.01
2008	19.22	14.57	0.12	17.81	18.49	-0.02
2009	23.02	25.17	-0.05	24.56	23.87	0.02
2010	18.97	26.61	-0.18	20.94	21.62	-0.02
Diabetes duration[4] (years) (mean ± SD)	5.58±2.69	5.36±2.58	0.08	5.53±2.69	5.59±2.54	-0.02
Medical history in past 1 year (%)						
Hypertension	44.18	52.58	-0.17	46.09	46.87	-0.02
Dyslipidemia	60.03	60.19	-0.00	60.67	60.18	0.01
Diabetic ketoacidosis	1.69	0.40	0.13	0.98	1.08	-0.01
Hyperosmolar hyperglycemic state	0.42	0.07	0.07	0.39	0.20	0.04
Hypoglycemia	1.01	0.69	0.04	1.08	1.17	-0.01
Depression	1.43	1.08	0.03	1.57	1.47	0.01
CIC category (%)						
Cancer	5.65	3.28	0.11	4.89	5.28	-0.02
Gastrointestinal	27.66	24.45	0.07	27.20	27.98	-0.02
Musculoskeletal	26.14	29.07	-0.07	26.03	27.98	-0.04
Pulmonary	6.49	4.65	0.08	5.68	5.87	-0.01
Substance abuse	2.61	1.30	0.10	2.15	2.25	-0.01
Mental illness	6.91	5.19	0.07	6.75	8.12	-0.05
Drug history in past 1 year (%)						

OADs						
Metformin	96.37	95.06	0.06	95.99	95.69	0.01
Sulfonylureas	95.78	94.37	0.07	95.30	95.79	-0.02
Meglitinides	8.60	8.69	-0.00	9.49	7.83	0.06
Thiazolidinediones	64.67	49.22	0.32	61.15	60.18	0.02
Alpha-glucosidase inhibitors	38.79	54.17	-0.31	42.47	41.59	0.02
Dipeptidyl peptidase-4 inhibitors	6.83	7.54	-0.03	7.14	8.71	-0.06
CVD-related medications						
Lipid-modifying agents	53.04	56.04	-0.06	54.31	55.28	-0.02
±-blockers	2.19	2.38	-0.01	2.45	2.05	0.03
β-blockers	18.21	20.74	-0.06	18.59	16.63	0.05
RAAS agents	30.52	36.53	-0.13	30.63	32.49	-0.04
Diuretics	11.97	13.16	-0.04	12.13	10.47	0.05
CCBs	21.67	30.65	-0.21	23.68	23.19	0.01
Class I and III antiarrhythmics	0.34	0.43	-0.02	0.29	0.49	-0.03
Digoxin	0.51	0.54	-0.00	0.59	0.29	0.04
Vasodilators	1.77	1.73	0.00	1.96	1.17	0.06
Antithrombotic agents	17.88	18.68	-0.02	18.40	16.73	0.04
A1c tests in past 1 year (mean ± SD)	3.26 ± 1.80	3.07 ± 1.89	0.11	3.23 ± 1.83	3.37 ± 1.94	-0.07
P4P (%)	34.91	17.85	0.39	29.06	28.28	0.02
Index agent[5] prescriber's specialty (%)						
Family medicine	13.07	24.41	-0.29	15.07	15.66	-0.02
Endocrinology	58.35	29.10	0.62	52.15	50.78	0.03
Internal medicine	17.71	24.77	-0.17	20.35	22.21	-0.05
Cardiology	1.77	7.86	-0.29	2.05	2.35	-0.02
Nephrology	0.93	3.07	-0.15	1.08	1.37	-0.03

Abbreviations: SD, standard deviation; SMD, standardized mean difference; CIC, chronic illness with complexity; OADs, oral antidiabetic drugs; CVD, cardiovascular disease; RAAS, renin-angiotensin-aldosterone system; CCB: calcium channel blocker; P4P, pay for performance.

1: Complication-free study cohort is defined as patients without diabetes-related complications (a) at one year before index date and (b) before stable use of fourth-line insulin in the fourth-line insulin users group and of enhanced OAD therapy in the PIC group.

2: SMD > 0.1 or SMD < -0.1 indicates significant difference in baseline characteristics between fourth-line insulin and PIC groups.

3: Index date is defined as the first date of insulin prescribed for fourth-line insulin users or the first date of three OADs' maximal doses reached/the first date of fourth-line OAD added on for PICs.

4: Diabetes duration was measured as the time from the first date of T2DM diagnosis to index date.

5: Index agent is denoted as the first insulin prescription for fourth-line insulin users or the first prescription of three OADs' maximal doses reached/fourth-line OAD added on for PICs.

Table 2: Incidence rates and hazard ratios of diabetes-related complications and death for fourth-line insulin users (fourth-line insulin) vs. potential insulin use candidates (PICs) after propensity score matching (primary analysis: complication-free study cohort[1])

Complications	Event/1,000 person-years		Fourth-line insulin vs. PICs HR (95%CI)	Hypoglycemia-adjusted HR (95%CI)	Akaike information criterion (AIC)	
	Fourth-line insulin (n = 1,022)	PICs (n = 1,022)			Without adjustment for hypoglycemia	With adjustment for hypoglycemia
CVD composite[2]	23.26	17.46	1.37 (0.99-1.89)	1.29 (0.93-1.80)	211.73	199.26
MI	2.05	3.31	0.67 (0.27-1.63)	0.60 (0.22-1.65)	28.92	25.17
Cerebrovascular diseases	10.20	7.03	1.40 (0.88-2.24)	1.18 (0.71-1.95)	99.80	88.15
MI + cerebrovascular diseases	11.93	10.23	1.22 (0.81-1.86)	1.08 (0.69-1.70)	124.47	107.85
Heart failure	4.67	2.94	1.64 (0.77-3.46)	1.66 (0.74-3.70)	40.50	38.67
Ischemic heart diseases	10.43	8.96	1.20 (0.77-1.88)	1.24 (0.78-1.96)	108.11	105.97
Peripheral vascular diseases	26.52	23.98	1.20 (0.91-1.58)	1.16 (0.87-1.53)	277.64	274.03
Hypoglycemia	20.26	13.80	1.45 (1.02-2.07)	NA	171.03	NA
All-cause death	5.75	3.47	1.53 (0.80-2.94)	1.23 (0.59-2.56)	52.98	43.89

Abbreviations: HR, hazard ratio; CVD, cardiovascular disease; MI, myocardial infarction; NA, not applicable.

1: Complication-free study cohort is defined as patients without diabetes-related complications (a) at one year before index date and (b) before stable use of fourth-line insulin in the fourth-line insulin users group and of enhanced OAD therapy in the PIC group.

2: CVD composite included myocardial infarction, cerebrovascular diseases, heart failure, ischemic heart disease, arrhythmia, arteriosclerotic cardiovascular disease, aortic aneurysm, cardiogenic shock, and cardiac arrest.

Table 3: Hazard ratios of diabetes-related complications and death for fourth-line insulin users (fourth-line insulin), fourth-line basal insulin users (fourth-line basal), fourth-line long-acting insulin analogs users (fourth-LA) vs. potential insulin use candidates (PICs) after propensity score matching (primary analysis: complication-free study cohort[1])

	Primary analysis	Subgroup analysis	
Complications	Fourth-line insulin vs. PICs HR (95% CI)	Fourth-line basal vs. PICs HR (95% CI)	Fourth-line LA vs. PICs HR (95% CI)
CVD composite[2]	1.37 (0.99-1.89)	1.00 (0.65-1.54)	0.89 (0.45-1.73)
MI + cerebrovascular diseases	1.22 (0.81-1.86)	0.76 (0.42-1.38)	0.65 (0.23-1.87)
Peripheral vascular diseases	1.20 (0.91-1.58)	1.14 (0.78-1.67)	1.01 (0.65-1.57)
Hypoglycemia	1.45 (1.02-2.07)	1.37 (0.85-2.19)	1.94 (0.88-4.26)
All-cause death	1.53 (0.80-2.94)	1.37 (0.55-3.42)	---*

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction.

1: Complication-free study cohort is defined as patients without diabetes-related complications (a) at one year before index date and (b) before stable use of fourth-line insulin (or basal insulin alone or long-acting insulin analogs alone) in the fourth-line insulin (or basal insulin or long-acting insulin analogs) users group and of enhanced OAD therapy in the PIC group. The group of patients initiating fourth-line basal insulin alone was a subgroup of patients initiating fourth-line insulin, and the group of patients initiating fourth-line long-acting insulin analogs alone was a subgroup of patients initiating fourth-line basal insulin alone.

2: CVD composite included myocardial infarction, cerebrovascular diseases, heart failure, ischemic heart disease, arrhythmia, arteriosclerotic cardiovascular disease, aortic aneurysm, cardiogenic shock, and cardiac arrest.

*HR could not be calculated due to a small number of events.