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Relationship between the early initiation of insulin treatment and diabetic complications in patients newly diagnosed with type 2 diabetes mellitus in Korea: A nationwide cohort study

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Keywords
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ABSTRACT

Aims/Introduction: To evaluate the relationship between early insulin initiation within a year after type 2 diabetes mellitus diagnosis and the risk of diabetic complications.

Materials and methods: We carried out a cohort study using the Korean National Health Insurance Service database. The study participants were newly diagnosed with type 2 diabetes mellitus between 2009 and 2013. After applying propensity score matching (1:1) to the cohort of patients who received two or more oral antidiabetic drugs (OADs) or insulin as the first prescription within 1 year after type 2 diabetes mellitus diagnosis, we computed hazard ratios (HRs) and 95% confidence intervals (CIs) using a Cox proportional hazards regression to compare the risk of diabetes-related microvascular and macrovascular complications and all-cause mortality in insulin versus OAD initiators.

Results: Within the cohort, 52,188 and 1,804 patients received OAD and insulin, respectively. After matching, each group contained 534 patients. Compared with the OAD group, the risk of overall microvascular complications was significantly higher for insulin (HR 1.48, 95% CI 1.28–1.71). No increased risks of overall macrovascular complications (HR 0.90, 95% CI 0.62–1.30) and all-cause mortality were observed (HR 1.06, 95% CI 0.67–1.68).

Conclusions: In the present study, early insulin treatment was not associated with the risk of macrovascular complications and all-cause mortality compared with OAD treatment; however, the risk of microvascular complications was higher in the insulin group.

INTRODUCTION

Insulin is an essential and potent glucose-lowering agent[1]. For patients with type 2 diabetes mellitus, insulin treatment can not only be considered after the failure of treatment with oral antidiabetic drugs (OADs), but also as the first treatment for patients with hemoglobin A1c levels >9.0% with symptomatic hyperglycemia or metabolic decompensation[2]. Several studies have shown that early intensive glucose control using insulin in newly diagnosed type 2 diabetes mellitus patients has favorable clinical effects, such as lowering glucotoxicity, improving β-cell function and restoring first-phase insulin secretion[3–5]. However, there is limited evidence regarding the long-term effect of early insulin treatment on diabetic complications, although the most fundamental and important goal of diabetes management is to delay or prevent complications[6].

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial was a landmark trial to investigate the long-term safety of early insulin initiation that reported a neutral effect on cardiovascular outcomes (hazard ratio [HR] 1.02, 95% confidence internal [CI] 0.94–1.11), microvascular outcomes (HR 0.97, 95% CI 0.90–1.05) and all-cause mortality (HR 0.98, 95% CI 0.90–1.08) compared with standard care[7]. However, that study was limited to patients with a cardiovascular risk factor and included only titrated basal insulin glargine as exposure among various insulin preparations, which hampered the generalization of the results. To the best of our

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knowledge, there have been no studies on the association between the early initiation of insulin treatment and the risk of diabetic complications in newly diagnosed type 2 diabetes mellitus using real-world data.

Thus, the present observational cohort study aimed to evaluate the relationship between early insulin treatment and the risk of diabetes-related microvascular and macrovascular complications and all-cause death in newly diagnosed type 2 diabetes mellitus patients using the Korean National Health Insurance Service (NHIS) database.

MATERIALS AND METHODS

Study design and data source

We carried out a retrospective cohort study using the Korean National Health Insurance Service (NHIS) data of randomly selected patients who examined national health checkup between 1 January 2009 and 31 December 2013 (sampling rate of 50%). The Korean NHIS database covers approximately 97% of the total Korean population, and includes information on eligibility, demographic characteristics (sex, age, residence and income level), medical history (diagnosis, procedures and prescription), medical health checkups (height, weight, body mass index, blood pressure, fasting glucose, cholesterol, liver function tests, kidney function tests, and questionnaires on lifestyle and behavior) and death verified by Statistics Korea. The medical health checkup information includes not only anthropometric variables, but also laboratory values that can confirm the severity of diabetes, such as fasting plasma glucose and various health indicators, such as lipid profile, blood pressure and estimated glomerular filtration rate.

Study population

We identified patients aged ≥20 years who were diagnosed with diabetes mellitus (International Classification of Disease-10 [ICD-10] codes: E11-14) or had a fasting plasma glucose level of ≥126 mg/dL between 2009 and 2013 (cohort entry). To restrict to incident diabetes patients, we excluded patients who did not have any antidiabetic medication prescription records between 1 January 2002 and cohort entry. Patients who initiated treatment with two or more OADs or insulin within 1 year after diagnosis were defined as the study participants. The first prescription date of the drugs of interest was defined as the index date. Patients who had the following conditions within 1 year before the index date were excluded: (i) those who had no history of prescription of antidiabetic drugs within 1 year from diagnosis (to improve the validity of the diabetes cohort); (ii) patients receiving insulin treatment during hospitalization (these patients have a higher risk of death)[8]; (iii) patients with gestational diabetes mellitus (ICD-10 code: O24); (iv) patients with type 1 diabetes mellitus (E10); (v) patients with any type of cancer (C00-C97); and (vi) patients with pancreatitis (K86.0 and K86.1), which might influence the choice of insulin and OAD treatment.

Exposure and outcome definition

OAD included biguanides, thiazolidinediones (TZD), sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitors and alpha-glucosidase inhibitors. Insulins are classified into premixed insulins, basal insulins and short-acting insulins. The Anatomical Therapeutic Chemical codes for insulin and OAD used in the present study are listed in Table S1. As we used the intention-to-treat method for the main analysis, exposure was determined based on the first prescription after the diagnosis of type 2 diabetes mellitus. The outcome of interest was microvascular and macrovascular complications, and all-cause mortality. The ICD-10 codes for diabetic complications are listed in Table S2. Patients were followed up from the index date to the occurrence of the outcome event or end of the study period (31 December 2018), whichever occurred first.

Potential confounders

We included the following potential confounding factors in the adjustment model: age, sex, income, chronic diseases (i.e., hypertension and dyslipidemia), body mass index, estimated glomerular filtration rate and lifestyle (i.e., smoking status, alcohol consumption and regular exercise), which were assessed during cohort entry. Prior comedications, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, antiplatelet and antithrombotic agents, prior macrovascular complications, such as other heart diseases (angina pectoris, arrhythmias, atrial fibrillation, and heart failure), artery diseases (atherosclerosis and aneurysm), ischemic heart disease, ischemic stroke, hemorrhagic stroke and percutaneous coronary intervention or coronary artery bypass graft, and prior microvascular complications, such as neuropathy, nephropathy and retinopathy, were identified during the 1-year baseline period before the index date. A study scheme for the selection of patients and assessment of covariates is shown in Figure S1.

Statistical analysis

Baseline characteristics are presented as means with standard deviations for continuous variables, and frequencies with percentages for categorical variables. To balance the baseline covariates between the two groups, we applied propensity score matching (1:1). The success of the matching procedure was evaluated by plotting the propensity score-distribution and tabulating the standardized difference of the baseline covariates. An absolute standardized difference of covariates <0.1 between the groups indicates a negligible difference in the mean or prevalence of the covariate. We also calculated the number of events, patient-years, and incidence rates in the OAD and insulin groups. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression analysis, and the level of significance was set at a *P*-value of 5%. The adjusted model included pre-specified confounders, duration of diabetes and time to first prescription from the diagnosis of diabetes. The time from the index date to the

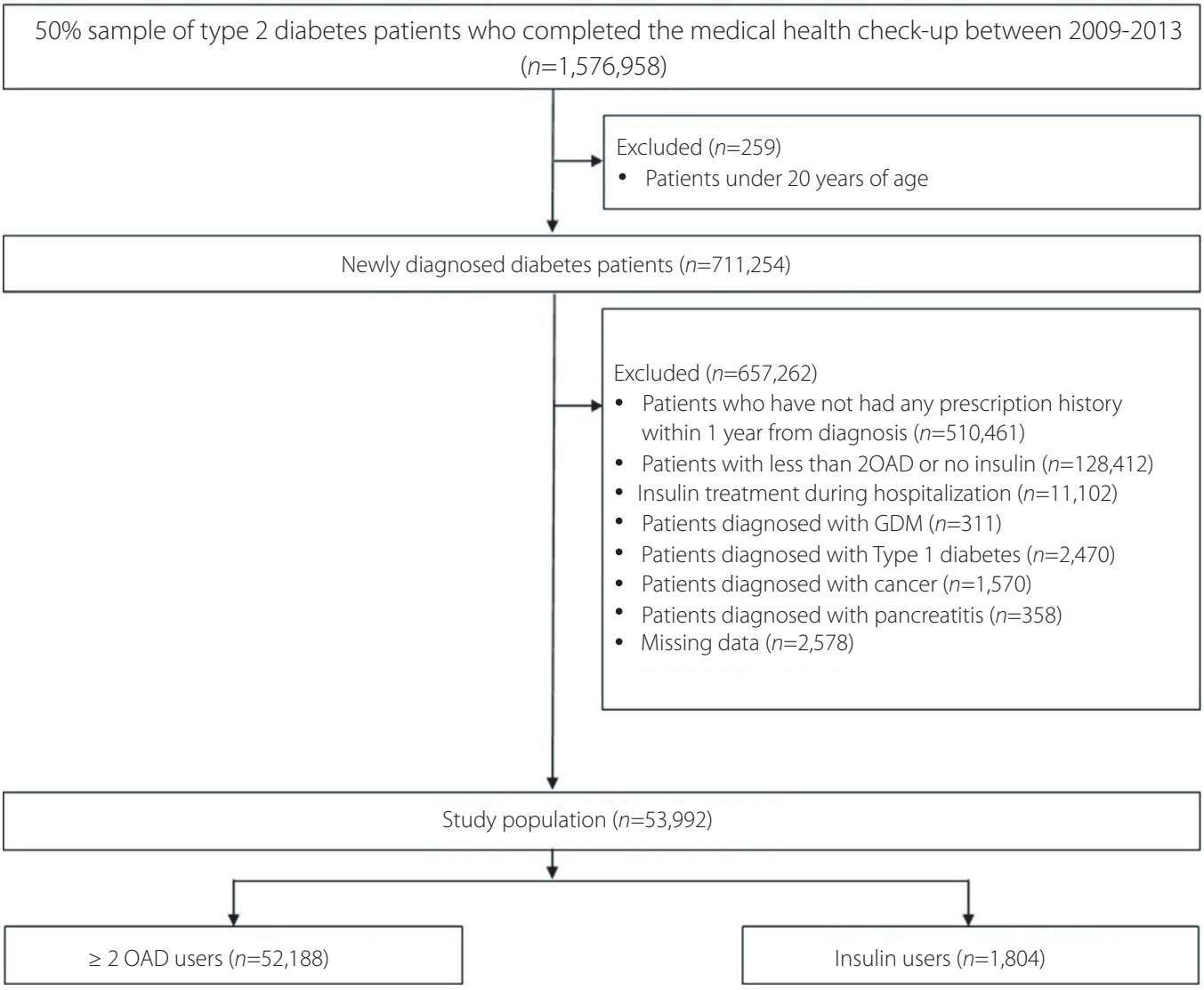

Figure 1 | Flow chart for the selection of the study population. OAD, oral antidiabetic drug; GDM, gestational diabetes mellitus.

incidence of the outcome event was visualized using Kaplan–Meier graphs. For sensitivity analyses, we applied censoring when patients initiated insulin treatment in the OAD group during the follow-up period. All analyses were carried out using SAS version 9.4. (SAS Institute, Cary, NC, USA).

Subgroup analysis

We carried out subgroup analyses according to the range of fasting plasma glucose (<160 mg/dL, 160–180 mg/dL and ≥180 mg/dL), initiation time of insulin treatment from diagnosis of diabetes (≤180 and 181–365 days), combination of OAD (metformin + sulfonylurea, metformin + DPP-4 inhibitor, metformin + TZD and other combinations), number of insulin prescriptions within 1 year after diagnosis (< 3, 3–10 and ≥10 times), exposure time of OAD within 1 year from the index date (<90 and ≥90 days) and type of insulin (premixed insulin, basal insulin, basal insulin + short-acting insulin and other insulin).

RESULTS

We identified 1,576,958 patients with diabetes mellitus who underwent medical health checkups between 2009 and 2013. After applying the exclusion criteria, a total of 53,992 patients remained; 52,188 were OAD initiators and 1,804 were insulin initiators (Figure 1). The mean age of the OAD users was 53.61 years (standard deviation 11.15), which was lower than that of the insulin users (51.67 (standard deviation 12.89) years; Table S3). Average fasting plasma glucose levels of insulin users were higher than that of the OAD users (215.97 ± 97.52 vs 189.93 ± 69.17). Regarding the previous experience of

microvascular complications that occurred 1 year before the index date, the proportions of neuropathy, nephropathy and retinopathy were 6.24, 3.63 and 3.28% in OAD users, and 11.2, 6.65 and 5.82% in insulin users, respectively. After matching, 534 patients remained in each group. Most of the baseline covariates were well balanced between the two groups (Table 1).

The risk of overall microvascular complications was higher in the insulin group than in the OAD group (HR 1.48, 95% CI 1.28–1.71; Table 2). The risks of the subtypes of microvascular complications were higher with insulin, but that of nephropathy was not statistically significant (neuropathy: HR 1.53, 95% CI 1.25–1.86; nephropathy: HR 1.17, 95% CI 0.92–1.49, and retinopathy: HR 1.39, 95% CI 1.15–1.68). There was no association between insulin use and overall macrovascular complications (HR 0.90, 95% CI 0.62–1.30) and all-cause mortality (HR 1.06, 95% CI 0.67–1.68). The results of the main outcomes of the Kaplan–Meier analysis are shown in Figure 2.

In the subgroup analysis, the risk of overall microvascular complications with insulin versus OAD remained higher in all subgroups (Figure 3). When the time from diagnosis to insulin initiation was divided into ≤180 days and 181–365 days, the adjusted HRs of overall microvascular complications in the insulin group were 1.36 (95% CI 1.26–1.48) and 1.61 (95% CI 1.43–1.82), respectively. As the number of insulin prescriptions increased, the risk of microvascular complications also increased. The risk was approximately twofold higher in the insulin group than in the OAD group, with a OAD exposure time of <90 days; however, the risk of overall macrovascular complications was significantly lower (HR 0.76, 95% CI 0.60–0.97). No increased risk was observed for the overall macrovascular complications. The risk of mortality was significantly higher in the insulin group when insulin treatment was initiated between 181 and 365 days after the index date (HR 1.60, 95% CI 1.16–2.21), and the combination of OAD was metformin plus sulfonylurea (HR

Table 1 | Baseline characteristics of patients with newly diagnosed type 2 diabetes after propensity score matching

Characteristics	Propensity matched patients (1:1)		aSD
	OAD users (n = 534)	Insulin users (n = 534)	
Age (years)	52.68 ± 11.36	52.8 ± 12.21	0.0105
Male sex	371 (69.48)	386 (72.28)	0.0617
Smoking status			
Never smoker	226 (42.32)	236 (44.19)	0.0378
Former smoker	121 (22.66)	96 (17.98)	0.1165
Current smoker	187 (35.02)	202 (37.83)	0.0584
Alcohol drinking (g/day)			
None	259 (48.5)	261 (48.88)	0.0076
Mild (<30)	214 (40.07)	207 (38.76)	0.0268
Heavy (≥30)	61 (11.42)	66 (12.36)	0.0290
Regular exercise[†]	90 (16.85)	80 (14.98)	0.0511
Income (lower 20%)	81 (15.17)	96 (17.98)	0.0756
BMI (kg/m^2)	25.18 ± 3.51	25.22 ± 3.64	0.0119
Fasting plasma glucose (mg/dL)	222.86 ± 101.02	224.54 ± 97.8	0.0169
SBP (mmHg)	128.29 ± 16.07	128.52 ± 16.52	0.0139
DBP (mmHg)	80.47 ± 10.82	80.93 ± 11.32	0.0414
Total cholesterol (mg/dL)	216.56 ± 46.55	220.49 ± 45.5	0.0854
GFR (mL/min/1.73 m^2)	91.68 ± 54.88	86.17 ± 23.04	0.1310
Comorbidity			
Hypertension[‡]	260 (48.69)	256 (47.94)	0.0150
Dyslipidemia[§]	254 (47.57)	261 (48.88)	0.0262
Use of glycemia drugs			
Metformin	503 (94.19)	504 (94.38)	0.0082
Sulfonylurea	386 (72.28)	393 (73.6)	0.0297
Meglitinides	20 (3.75)	23 (4.31)	0.0285
TZD	36 (6.74)	34 (6.37)	0.0150
DPP-4 inhibitor	75 (14.04)	82 (15.36)	0.0373
AGI	87 (16.29)	74 (13.86)	0.0680
Prior comedication[††]			
Prior ACE inhibitor	27 (5.06)	32 (5.99)	0.0407
Prior ARB	135 (25.28)	134 (25.09)	0.0044
Prior statin	184 (34.46)	176 (32.96)	0.0317
Prior anti-platelet	134 (25.09)	129 (24.16)	0.0216
Prior anti-thrombotic agents	0 (0)	2 (0.37)	0.0862
Prior macrovascular complication[††]			
Other heart disease[‡‡]	42 (7.87)	46 (8.61)	0.0269
Artery disease[§§]	16 (3)	13 (2.43)	0.0351
Ischemic heart disease	41 (7.68)	38 (7.12)	0.0214
Ischemic stroke	18 (3.37)	20 (3.75)	0.0205
Hemorrhagic stroke	1 (0.19)	2 (0.37)	0.0341
PCI or CABG	1 (0.19)	1 (0.19)	0.0000
Prior microvascular complication[††]			
Neuropathy	50 (9.36)	63 (11.8)	0.0794
Nephropathy	19 (3.56)	24 (4.49)	0.0473
Retinopathy	17 (3.18)	25 (4.68)	0.0773

Values are presented as numbers (%) and mean ± standard deviation. ACE, angiotensin converting enzyme; AGI, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; aSD, absolute standardized difference; BMI, body mass index; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; OAD, oral antidiabetic drug; PCI, percutaneous coronary intervention; SD, standard deviation; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione. [†]Regular exercise was defined as performing >30 min of moderate physical activity at least 5 times per week or >20 min of strenuous physical activity at least three times per week. [‡]Hypertension was defined as (International Classification of Disease-10 code [I10, I11, I12, I13, I15] and medication) or systolic blood pressure (SBP) ≥140 or diastolic blood pressure (DBP) ≥90. [§]Dyslipidemia was defined as (International Classification of Disease-10 code [E78 & medication] or total cholesterol ≥240. Prescription records at the index date. [††]Within 1 year before the index date. [‡‡]Other heart diseases included angina pectoris, arrhythmias, atrial fibrillation and heart failure. [§§]Artery disease includes atherosclerosis and aneurysm.

Table 2 | Hazard ratios of diabetic complications and all-cause mortality in patients who initiated insulin treatment as a first prescription compared with patients that initiated two or more oral antidiabetic drugs as first prescription after propensity score matching

	No. events	Patient years	IR/1,000PY	Adjusted HR† (95% CI)	*P*-value
Overall microvascular complication					
OAD	321	2,125	151.09	Reference	<.0001
Insulin	402	1,720	233.77	1.48 (1.28–1.71)	
Neuropathy					
OAD	169	2,965	57.01	Reference	<.0001
Insulin	236	2,645	89.24	1.53 (1.25–1.86)	
Nephropathy					
OAD	124	3,216	38.55	Reference	0.1976
Insulin	148	3,321	44.57	1.17 (0.92–1.49)	
Retinopathy					
OAD	190	2,868	66.25	Reference	0.0006
Insulin	253	2,756	91.80	1.39 (1.15–1.68)	
Overall macrovascular complication					
OAD	59	3,566	16.54	Reference	0.5752
Insulin	56	3,736	14.99	0.90 (0.62–1.30)	
Stroke					
OAD	17	3,720	4.57	Reference	0.3869
Insulin	13	3,917	3.32	0.73 (0.35–1.50)	
MI					
OAD	10	3,748	2.67	Reference	0.9406
Insulin	10	3,920	2.55	0.97 (0.40–2.33)	
PCI					
OAD	14	3,707	3.78	Reference	0.7641
Insulin	16	3,880	4.12	1.12 (0.55–2.29)	
CABG					
OAD	0	3,774	0.00	Reference	-
Insulin	1	3,959	0.25	N/A	
ICH					
OAD	2	3,766	0.53	Reference	0.7062
Insulin	3	3,955	0.76	1.41 (0.24–8.45)	
IHD					
OAD	46	3,608	12.75	Reference	0.8219
Insulin	46	3,760	12.23	0.95 (0.63–1.44)	
All-cause mortality					
OAD	34	3,774	9.01	Reference	0.8021
Insulin	39	3,959	9.85	1.06 (0.67–1.68)	

CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhagic stroke; IR, incidence rate; MI, myocardial infarction; N/A, not available; OAD, oral antidiabetic drug; PY, patient years; T2DM, type 2 diabetes mellitus. †Adjusted for age, sex, income, hypertension, dyslipidemia, smoking status, alcohol drinking, regular exercise, body mass index, fasting plasma glucose, glomerular filtration rate, other heart disease, artery disease, ischemic heart disease (IHD), stroke, ICH, percutaneous coronary intervention (PCI), neuropathy, nephropathy, retinopathy, sulfonylurea, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor, diabetes duration, prior antiplatelet therapy, prior antithrombotic agents and time to first prescription from the diagnosis of diabetes.

1.41, 95% CI 1.18–1.68), DPP-4 inhibitor (HR 1.79, 95% CI 1.46–2.19) and TZD (HR 1.81, 95% CI 1.38–2.39). When patients who switched from OAD treatment to insulin were censored, the results were found to be mostly consistent with the main results, except for a higher risk of all-cause mortality (HR 1.52, 95% CI 1.20–1.92; Table S4).

DISCUSSION

In the present cohort study, the risk of overall microvascular complications significantly increased with early insulin use compared with the use of two or more OADs. There was no association between insulin use and the risk of overall macrovascular complications or all-cause mortality. In the subgroup analyses, compared with the OAD group, whose exposure time was <90 days from the index date, the insulin group showed a significantly lower risk of macrovascular complications. The risk of all-cause mortality was significantly higher in the insulin group than in the group with a relatively late initiation of insulin from diagnosis and a certain combination of OADs.

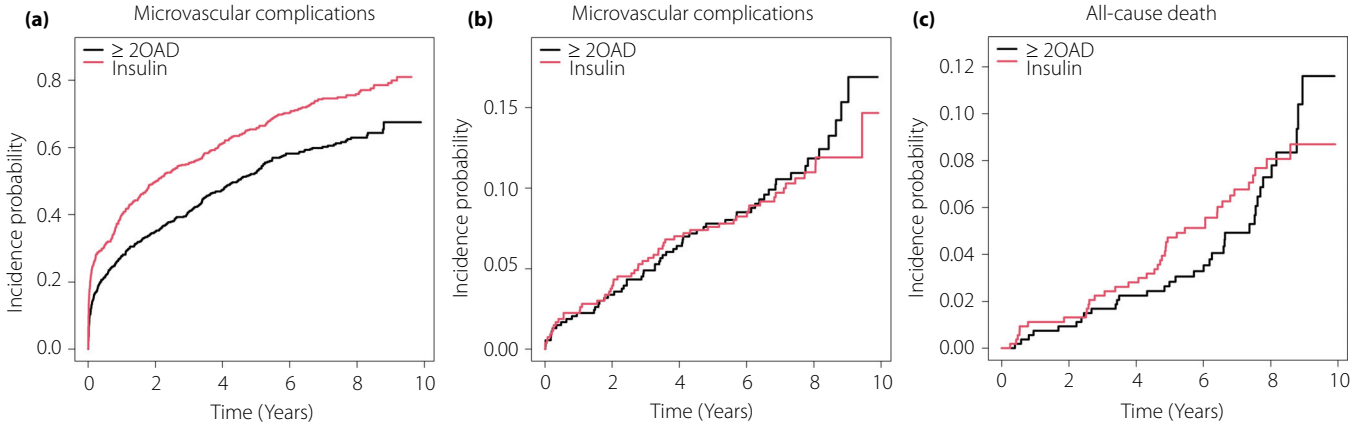

Figure 2 | Kaplan–Meier curves and adjusted hazard ratios of the main analysis (≥2 oral antidiabetic drugs [OAD] group vs insulin group for the propensity score-matched cohort) for (a) overall microvascular complications, (b) overall macrovascular complications and (c) all-cause mortality.

Subgroup	Overall microvascular complications Adjusted HR (95% CI)	Overall microvascular complications Adjusted HR (95% CI)	All-cause mortality Adjusted HR (95% CI)
Fasting plasma glucose, mg/dL			
< 160	1.37 (1.21-1.56)	0.99 (0.75-1.32)	1.32 (0.95-1.85)
160-180	1.61 (1.25-2.07)	0.69 (0.33-1.41)	0.69 (0.28-1.72)
≥180	1.41 (1.29-1.55)	0.93 (0.71-1.22)	1.06 (0.75-1.48)
Initiation time of insulin,days			
≤180	1.36 (1.26-1.48)	0.96 (0.78-1.18)	1.08 (0.84-1.39)
181-365	1.61 (1.43-1.82)	1.00 (0.74-1.36)	1.60 (1.16-2.21)
Combination of OAD			
MET+SU	1.29 (1.22-1.37)	0.98 (0.85-1.14)	1.41 (1.19-1.66)
MET+DPP4i	1.33 (1.25-1.42)	1.07 (0.92-1.26)	1.62 (1.34-1.96)
MET+TZD	1.33 (1.22-1.44)	1.12 (0.91-1.38)	1.68 (1.31-2.16)
Others	1.28 (1.11-1.47)	1.03 (0.74-1.44)	1.07 (0.72-1.59)
No. of insulin prescription, times			
< 3	1.33 (1.23-1.44)	0.99 (0.81-1.21)	1.21 (0.95-1.54)
3-10	1.59 (1.43-1.78)	0.88 (0.64-1.22)	1.20 (0.82-1.74)
≥10	2.01 (1.54-2.63)	0.62 (0.26-1.52)	0.47 (0.15-1.47)
Exposure time of OAD, days			
< 90	2.05 (1.87-2.25)	0.76 (0.60-0.97)	0.79 (0.60-1.05)
≥90	1.27 (1.17-1.36)	0.97 (0.80-1.17)	1.22 (0.96-1.55)
Type of insulin			
Premixed insulin	1.23 (1.05-1.45)	0.88 (0.55-1.42)	1.35 (0.82-2.24)
Basal insulin	1.42 (1.31-1.53)	0.94 (0.76-1.15)	1.08 (0.84-1.39)
Basal insulin+SAI	1.58 (1.28-1.95)	1.06 (0.57-1.95)	1.18 (0.57-2.43)
Others	1.59 (1.30-1.94)	1.03 (0.66-1.60)	1.58 (1.01-2.46)

Figure 3 | Subgroup analysis of overall microvascular and macrovascular complications and all-cause mortality among patients who received early insulin treatment compared with those who received oral antidiabetic drugs. CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitor; HR, hazard ratio; MET, metformin; OAD, oral antidiabetic drug; SAI, short-acting insulin; SU, sulfonylurea; TZD, thiazolidinedione.

In the ORIGIN trial, early use of insulin glargine did not increase the risk of cardiovascular events (myocardial infarction and stroke) and death from cardiovascular causes (adjusted HR 1.02, 95% CI 0.94–1.11) and all-cause mortality (adjusted HR 0.98, 95% CI 0.90–1.08) compared to standard care[7]. Furthermore, a higher risk of microvascular complications was not observed (adjusted HR 0.97, 95% CI 0.90–1.05), which was inconsistent with the present results. This discrepancy might be due to the difference in glucose control status between the two studies. The median fasting plasma glucose of the insulin group in this study was higher than that in the ORIGIN trial (225 mg/dL vs 125 mg/dL). Patients in the present study might be subject to tighter glucose control with high doses of insulin, but might not have reached adequate glucose levels, because they could not receive regular monitoring in routine practice compared with the randomized controlled trial setting.

No observational studies have compared the risk of diabetic complications between early insulin treatment and OAD use as a first prescription in newly diagnosed type 2 diabetes mellitus patients using real-world data. However, two studies compared the risk of cardiovascular events and all-cause mortality in OAD-treated patients and insulin-treated patients with type 2 diabetes mellitus. Nystrom *et al.* compared the risk of cardiovascular events and all-cause mortality between patients who used insulin or DPP-4 inhibitors as a second-line treatment after metformin monotherapy using the Swedish prescribed drug national registry database[9]. The risk of cardiovascular events (HR 1.39, 95% CI 1.21–1.61) and all-cause mortality (HR 1.69, 95% CI 1.45–1.96) were significantly increased in patients treated with insulin compared with those treated with DPP-4 inhibitors. They also reported a higher risk of hypoglycemia (HR 4.35, 95% CI 2.26–8.35). One possible explanation of the different findings is the launch and use of second-generation insulin formulations as of 2015. As the study periods of the two studies differed (2007–2014 for Swedish study vs 2009–2018 for the present study), the use of second-generation insulins that improved hypoglycemia would have affected the results[10–12]. Severe hypoglycemia is associated with cardiovascular events and mortality[13–16].

Cheng *et al.* found an increased risk of all-cause mortality when they compared patients initiating DPP-4 inhibitors or TZD with those initiating basal insulin as an additional third agent after dual OAD combination therapy[17]. The lack of association between insulin use and all-cause mortality in the present study might be explained by the fact that our study was based on the first prescription after type 2 diabetes mellitus diagnosis. In our matched cohort, the fasting plasma glucose level was high, which represents a relatively hyperglycemic state. Insulin, as a potent glucose-lowering agent, might reduce glucotoxicity more rapidly than OAD in first drug users, which could have contributed to no higher risk of death.

Relatively late initiation of insulin (>180 days after diagnosis) was found to be associated with an increased risk of all-cause mortality compared with OAD, whereas no mortality risk was observed in patients who initiated insulin therapy within 180 days after diagnosis. As type 2 diabetes mellitus is a progressive disease, timely management of diabetes is highly recommended to maintain optimal glycemic control[18,19]. There is substantial evidence regarding the beneficial effects of timely insulin use; early insulin therapy can lead to recovery of residual pancreatic β-cell function and even durable remission of dysglycemia[20,21]. Notably, these findings are supported by the findings of the present study.

The present study had two strengths. First, our results can be generalized to real-world populations relative to those from randomized controlled trials. By using a population-based nationwide database, we could include a wide range of type 2 diabetes mellitus patients. According to Mauricio *et al.*, if insulin-using patients in real practice wanted to participate in randomized controlled trial studies, just 17% would be eligible due to the strict inclusion and exclusion criteria[22]. Second, we used the NHIS data of national health checkup examinees. The use of health checkup information can complement the limitations of claims data, because we can identify and adjust for various health indicators that could act as important covariates, such as fasting plasma glucose, body mass index, smoking status, alcohol consumption and degree of exercise. In particular, for diabetes studies, these indicators could play a key role in explaining the association between a drug and health outcomes due to the nature of metabolic diseases. Third, we could reduce confounding by the duration of diabetes by including patients who were newly diagnosed with type 2 diabetes mellitus and received insulin or OAD within 1 year after the diagnosis. Duration of diabetes is a potent risk factor for diabetic complications. By including incident type 2 diabetes mellitus patients, the mean disease duration before the index date would be <1 year and might not be largely different between the two groups. In addition, we adjusted the duration of diabetes, which is the time from the diagnosis of type 2 diabetes mellitus to the end of follow up, to minimize the confounding effect of disease duration.

The present study had several limitations. First, we could not include the hemoglobin A1c value, which is a glycemic index for the average level of blood sugar for the past 2–3 months and aids in the selection of diabetes treatment options; this is because the variable did not exist in our database. However, its exclusion from the study did not have a significant impact on the results, as the fasting plasma glucose included in the model is highly correlated with hemoglobin A1c[23]. Second, the accuracy of diagnostic codes might be low, because the NHIS database was established for administrative purposes and not research purposes. To enhance the validity of the study population, we excluded patients who did not have any records of prescriptions within a year after the diagnosis of diabetes. Furthermore, a previous study validating the diagnostic codes of cardiovascular diseases in the NHIS database reported that positive predictive values of diagnostic codes for acute myocardial infarction, stroke and intracerebral brain hemorrhage, which

were captured as macrovascular complications in that study, were quite high (71.0–70.0%)[24]. Finally, although we applied matching using propensity scores and adjusted for various covariates from health checkup data, residual confounders might still remain.

In summary, the results of the present cohort study showed no association between early insulin use and the risk of macrovascular complications and all-cause mortality compared with OAD use, although the risk of microvascular complications increased with insulin use. In the subgroup analysis, late use of insulin from the first diagnosis of diabetes was associated with a higher mortality risk. When initiating insulin as the first treatment for newly diagnosed type 2 diabetes mellitus patients in real practice, physicians need to consider the potential risk of microvascular complications and provide timely treatment.

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DISCLOSURE

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Approval of the research protocol: N/A.

Informed consent: This study was approved by the Institutional Review Board of Sungkyunkwan University (SKKU 2020-10-023). The IRB waived the requirement for informed consent from participants because of the retrospective design of the study.

Approval date of registry and the registration no. of the study/-trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Anatomical Therapeutic Chemical code for the insulin and oral antidiabetic drugs used in the present study.

Table S2 | International Classification of Disease-10 codes of diabetic complications.

Table S3 | Baseline characteristics of patients newly diagnosed with type 2 diabetes before propensity score matching.

Table S4 | Hazard ratios of the incidence of diabetic complications and all-cause mortality in the insulin group versus the oral antidiabetic drug group after censoring of patients who initiated insulin therapy in the oral antidiabetic drug group during the follow-up period.

Figure S1 | Study scheme showing the selection of patients and assessment of covariates.