Risk of early mortality and cardiovascular disease according to the presence of recently diagnosed diabetes and requirement for insulin treatment: A nationwide study

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ABSTRACT
Aims/Introduction: We estimated the hazards of cardiovascular diseases (CVDs) and early all-cause mortality in Korean adults according to the presence of recently diagnosed type 2 diabetes (type 2 diabetes for <5 years) and insulin use.

Materials and Methods: We used the Korean National Health Insurance Service–National Sample Cohort database (2002–2015) for this longitudinal population-based study. Among adults aged ≥40 years without baseline CVD, individuals without diabetes or with recently diagnosed type 2 diabetes were selected (N = 363,919). The hazard ratios (HRs) for myocardial infarction (MI), stroke, and all-cause mortality during follow-up were analyzed according to three groups categorized by the presence of type 2 diabetes and insulin use.

Results: Within a mean 7.8 years, there were 5,275 MIs, 7,220 strokes, and 15,834 deaths. The hazards for outcomes were higher in the insulin-treated type 2 diabetes group than in the non-diabetes group [HR (95% CI): 2.344 (1.870–2.938) for MI, 2.420 (1.993–2.937) for stroke, and 3.037 (2.706–3.407) for death], higher in the non-insulin-treated type 2 diabetes group than in the non-diabetes group [HR (95% CI): 1.284 (1.159–1.423) for MI, 1.435 (1.363–1.511) for stroke, and 1.135 (1.067–1.206) for death], and higher in the insulin-treated type 2 diabetes group than in the non-insulin-treated type 2 diabetes group [HR (95% CI): 1.914 (1.502–2.441) for MI, 1.676 (1.363–2.060) for stroke, and 2.535 (2.232–2.880) for death].

Conclusions: Recently diagnosed type 2 diabetes patients showed increased risks of incident CVDs and premature mortality, and insulin-treated group demonstrated an additional increase in the risks of these outcomes in adults with recently diagnosed type 2 diabetes, suggesting the need for intensified cardio-protective interventions for adults with insulin-treated type 2 diabetes.

INTRODUCTION
Diabetes imposes a burden on society in the form of decreases in labor force participation and productivity and premature mortality due to its potentially fatal complications, including cardiovascular disease. Previous studies consistently reported an increased risk of cardiovascular and premature all-cause death associated with diabetes. In our previous report, people with type 2 diabetes had an approximately 42% higher hazard of myocardial infarction (MI) and a 51% higher hazard of all-cause death compared to the population without diabetes within the mean follow-up of 4.6 years.
In the real-world, requirement for insulin treatment in people with type 2 diabetes might be associated with increased risk of cardiovascular events and/or early mortality although previous randomized controlled trials (RCTs) that compared insulin to other regimens demonstrated no significant increase in these outcomes in insulin groups. This is because, in the real-world, not the randomized controlled setting, individuals with type 2 diabetes requiring insulin treatment based on the decisions of clinicians may have different risk profiles of early all-cause mortality and cardiovascular disease compared to the individuals with non-insulin-treated type 2 diabetes. Nevertheless, to the best of our knowledge, previous real-world studies that considered the requirement for insulin treatment as a factor for predicting cardiovascular outcomes and early all-cause mortality that included only people with type 2 diabetes are still scarce, despite potential heterogeneity in hypoglycemia risk, glycemic variability, residual beta-cell function, and insulin resistance, according to the requirement for insulin treatment in people with type 2 diabetes. Although few studies have explored this aforementioned association among people with type 2 diabetes in non-randomized settings, their results were not applicable to the overall population with type 2 diabetes in general due to their restricted study populations, non-discrimination between diabetes type (type 1 vs type 2), lack of information on diabetes duration, marked variance in diabetes duration between groups classified by insulin treatment, and limited treatment regimens. Therefore, to explore whether risk profiles of cardiovascular diseases and early all-cause mortality vary between individuals with type 2 diabetes required vs not required to be treated with insulin in the real-world, we compared the risk for cardiovascular diseases (MI and stroke) and all-cause mortality during follow-up according to the presence of type 2 diabetes and insulin use through a real-world nationwide cohort study.

MATERIALS AND METHODS

Data sources

Data from the Korean National Health Insurance Service–National Sample Cohort (NHIS-NSC) database from January 2002 to December 2015 were used for this study. All residents in Korea are covered by the Korean National Health Insurance Service (NHIS), the single-insurer system in Korea. Information associated with healthcare utilization and prescriptions is recorded and stored by the NHIS. This information includes anonymous identification numbers, demographics, monthly household income, primary and secondary diagnoses classified according to the International Classification of Diseases-10th Revision (ICD-10), prescriptions, procedures, and dates of hospital visits and hospitalizations for all Korean residents. The NHIS-NSC was constructed by the Korean NHIS as a representative population-based sample cohort providing researchers and policy makers with representative datasets with a substantial volume that does not require privacy regulation. From the target population of 48,222,537 individuals that comprised the entire cohort enrolled in the Korean NHIS in 2006, a representative sample cohort of approximately one million was randomly selected using systematic stratified random sampling with proportional allocation within each stratum. These strata were constructed according to variables including age group, sex, residential area (metropolitan, urban, or rural), and income level. Records related to the healthcare utilization of this sample cohort beginning in January 2002 were compiled into NHIS-NSC datasets. This cohort was followed until December 2015, with the exception of participants whose eligibility was disqualified due to death or emigration.

The Institutional Review Board (IRB) of Korea University approved this study (IRB file number 2018GR0412). An informed consent exemption was granted by the IRB because the NHIS provided the researchers with anonymous, de-identified data.

Study cohort, outcomes, and follow-up

In this longitudinal population-based study, individuals aged ≥40 years, either without diabetes or with recently diagnosed type 2 diabetes (type 2 diabetes for <5 years), were selected from the NHIS-NSC in 2008 (Figure 1). The index year of 2008 was considered as the baseline. Individuals with any malignancy and those who received organ transplantation throughout all study periods were excluded. In addition, patients with a history of MI or stroke at or before the index year (2008) were also excluded. To unify the type and duration of diabetes, people with T1D (defined according to previous reports) and those with type 2 diabetes duration of ≥5 years were excluded from analysis.

The outcome variables were incident MI, stroke, and all-cause death during follow-up. According to previous studies, MI was defined as the recording of ICD-10 codes I21 or I22 during hospitalization or at least two claims under those codes, while stroke was defined as the recording of ICD-10 codes I63 or I64 during hospitalization with claims for brain magnetic resonance imaging or brain computed tomography. The study population was followed from baseline until the date of death, development of endpoint disease, or December 31, 2015, whichever came first.

Measurements and definitions

The presence of diabetes was assessed at baseline for all participants. According to previous studies, type 2 diabetes was defined as the recording of at least one claim per year for the prescription of antidiabetic drugs under ICD-10 codes E11–14 or a fasting plasma glucose concentration ≥126 mg/dL, excluding any persons with claims under ICD-10 code E10. Individuals who did not satisfy the definition of type 2 diabetes were classified into the non-diabetes group as those with T1D were already excluded from analyses. Insulin use (insulin treatment) was defined for all participants as at least one prescription of insulin per year and a total of at least three prescriptions of insulin in an outpatient setting. Participants...
were divided into the following three groups according to the presence of recently diagnosed type 2 diabetes and insulin use: no diabetes, non-insulin-treated type 2 diabetes, and insulin-treated type 2 diabetes.

Presence of hypertension\textsuperscript{15}, dyslipidemia\textsuperscript{15}, atrial fibrillation (AF)\textsuperscript{4,19,20}, hospitalization for heart failure (hHF)\textsuperscript{4,21,22}, dementia\textsuperscript{23,24}, and end-stage renal disease (ESRD)\textsuperscript{14} were defined according to previous studies. Charlson Comorbidity Index (CCI) was calculated according to the established method\textsuperscript{25,26} based on the diagnostic codes provided in previous reports\textsuperscript{7,28}. Low-income level was assigned to the lowest 20% of the entire population based on monthly household income.

Statistical analyses

The statistical analyses were conducted using SAS software (Version 9.3, SAS Institute, Cary, NC, USA). Two-tailed $P$-values of $<0.05$ were considered significant. Baseline characteristics are presented according to the three groups categorized by the presence of recently diagnosed type 2 diabetes and insulin use (non-diabetes group, non-insulin-treated type 2 diabetes group, and insulin-treated type 2 diabetes group). Continuous variables are expressed as means ± standard deviations, and categorical values are presented as frequencies and percentages. The incidence rates of MI, stroke, and all-cause mortality during follow-up were estimated using the number of incident cases divided by the follow-up duration in person-years. The cumulative incidence of these outcomes according to the three groups categorized by the presence of recently diagnosed type 2 diabetes and insulin use was estimated using Kaplan-Meier curves; the differences among groups were evaluated using the log-rank test. Cox regression analyses were performed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the incidence of MI, stroke, and all-cause mortality during follow-up according to the three pre-specified groups based on the diabetes status and insulin use. The proportional hazard assumption of the Cox models was ensured by the Schoenfeld residuals. Three regression models were constructed for these analyses: the crude (unadjusted) model, the age and sex-adjusted model, and the multivariable-adjusted model, adjusted for age, sex, monthly income, and CCI.

RESULTS

Baseline characteristics of the study population

The study population consisted of a total of 363,919 subjects (Figure 1). Among these, 348,152 had no diabetes, and 15,767 had recently diagnosed type 2 diabetes (duration $<5$ years). Of these 15,767 people with recently diagnosed type 2 diabetes, 14,397 were insulin non-users, and the remaining 1,370 were insulin users. The baseline characteristics of the study population are presented according to the three groups created by the presence of recently diagnosed type 2 diabetes and insulin treatment (Table 1). As the groups advanced from non-diabetes to non-insulin-treated type 2 diabetes to insulin-treated type 2 diabetes, a trend of increase in the mean age, proportion of individuals aged $\geq 65$ years and with low-income level, and prevalence of hypertension, dyslipidemia, AF, hHF, dementia, and ESRD was observed.

Incidence of cardiovascular disease and all-cause mortality during follow-up according to the presence of recently diagnosed type 2 diabetes and insulin use

During a mean follow-up of 7.79 ± 1.05 years (2,833,111.00 person-years), 5,275 MI cases developed, whereas 7,220 cases of stroke occurred during a mean follow-up of 7.77 ± 1.09 years (2,827,787.58 person-years). During a mean follow-up of 7.83 ± 0.93 years (2,850,265.46 person-years), 15,834 deaths were observed in the entire cohort. The cumulative incidence of MI, stroke, and all-cause death during follow-up is presented according to the three groups of diabetes status and insulin use using Kaplan-Meier curves (Figure 2). The incidence rates of MI, stroke, and all-cause death during follow-up were higher in people with type 2 diabetes (insulin users and non-users)
comparing to those without diabetes (Figure 2, Table 2). People with insulin-treated type 2 diabetes had higher incidence rates of MI, stroke, and all-cause mortality during follow-up than those with non-insulin-treated type 2 diabetes (Figure 2, Table 3).

The HRs (95% CIs) for incident MI, stroke, and all-cause death during follow-up were calculated with respect to the three groups according to diabetes status and insulin use (Table 2). In all models including the multivariable-adjusted model, the hazards of incident MI, stroke, and all-cause death during follow-up were higher among people with type 2 diabetes (insulin users and non-users) than among people without diabetes. In the multivariable-adjusted model, which was adjusted for age, sex, monthly income, and CCI, the HRs (95% CIs) in the non-insulin-treated type 2 diabetes compared with the non-diabetes group were 1.284 (1.159–1.423) for MI, 1.343 (1.320–1.561) for stroke, and 1.135 (1.067–1.206) for all-cause death during follow-up. The HRs (95% CIs) in the insulin-treated type 2 diabetes group compared with the diabetes group were 2.344 (1.870–2.938) for MI, 2.420 (1.993–2.937) for stroke, and 3.037 (2.706–3.407) for all-cause death during follow-up.

When the people with non-insulin-treated type 2 diabetes were set as the reference (Table 3), the HRs (95% CI) of incident MI, stroke, and all-cause death during follow-up among those with insulin-treated type 2 diabetes showed significantly higher values of 1.914 (1.502–2.441) for MI, 1.676 (1.363–2.060) for stroke, and 2.535 (2.232–2.880) for all-cause death during follow-up in the multivariable-adjusted model.

As an additional analysis, only individuals either without diabetes or with longer-standing type 2 diabetes (type 2 diabetes for ≥5 years) were selected, and HRs (95% CIs) for the incidence of MI, stroke, and all-cause mortality during follow-up were calculated according to the three pre-specified groups based on the diabetes status and insulin use (Table S1). This additional analysis showed results consistent with those from the main analysis.

**DISCUSSION**

In this nationwide longitudinal study including 363,919 individuals either with no diabetes or with recently diagnosed type 2 diabetes (diabetes duration <5 years), individuals with insulin-treated type 2 diabetes had a higher hazard of MI, stroke, and all-cause mortality during follow-up compared with those with non-insulin-treated type 2 diabetes or no diabetes. These findings were consistent after adjusting for age, sex, monthly income, and CCI.

Increased risks of cardiovascular and early all-cause mortality in people with diabetes have been consistently documented in previous studies. People with type 2 diabetes from the Swedish National Diabetes Register showed a 15% increased risk of all-cause death and a 14% increased risk of cardiovascular mortality compared to the age, sex, and county-matched controls during a mean follow-up of <5 years (mean 4.6 years in the diabetes group and 4.8 years in the control group). In the current study, people with non-insulin-treated type 2 diabetes were at a 13.5% increased hazard of all-cause death during follow-up compared to the non-diabetes population, which is similar to an overall 15% increased risk in people with type 2 diabetes from the Swedish National Diabetes Register compared to controls without diabetes. However, individuals with insulin-treated type 2 diabetes showed a much higher 3.037-fold (203.7%) increased hazard of all-cause death during follow-up compared to the non-diabetes controls in the current study.

Insulin-treated patients compared to those without insulin treatment had a significantly higher hazard of MI, stroke, and all-cause mortality during follow-up among people with type 2 diabetes in this real-world study. This finding suggests that people with insulin-treated type 2 diabetes should be considered as...
a population with higher risk for cardiovascular disease and early all-cause mortality, and related monitoring and cardio-
protective interventions should be focused on this population
to reduce the social burden associated with these fatal compli-
cations. Few previous studies have evaluated insulin use as a
predictor of cardiovascular outcomes and all-cause mortality.

Figure 2 | Cumulative incidence of myocardial infarction, stroke, and all-cause death during follow-up according to the presence of diabetes and insulin use. Only those with diabetes duration of <5 years were included among people with type 2 diabetes.

Table 2 | Hazard ratios and 95% confidence intervals for the incidence of myocardial infarction, stroke, and all-cause death during follow-up, according to the presence of diabetes and insulin use among individuals either without diabetes or with recently diagnosed type 2 diabetes (diabetes for <5 years)

| Group | Events | Follow-up duration (person-years) | Incidence rate (per 1000 person-years) | Unadjusted | Age and sex-adjusted | Multivariable adjusted* |
|-------|--------|----------------------------------|----------------------------------------|------------|----------------------|-------------------------|
| Myocardial infarction | | | | | | |
| No diabetes (n = 348,152) | 4,749 | 2,714,833.85 | 1.74098 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Type 2 diabetes, insulin non-user† (n = 14,397) | 445 | 109,030.08 | 4.08144 | 2.334 (2.117, 2.572) | 1.589 (1.441, 1.751) | 1.284 (1.159, 1.423) |
| Type 2 diabetes, insulin user† (n = 1,370) | 81 | 9,247.07 | 8.75953 | 5.017 (4.029, 6.248) | 3.360 (2.698, 4.186) | 2.344 (1.870, 2.938) |
| P for trend | <0.0001 | <0.0001 | <0.0001 |
| Stroke | | | | | | |
| No diabetes (n = 348,152) | 6,437 | 2,710,183.97 | 2.37510 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Type 2 diabetes, insulin non-user† (n = 14,397) | 673 | 108,423.56 | 6.20710 | 2.615 (2.416, 2.832) | 1.685 (1.556, 1.825) | 1.435 (1.320, 1.561) |
| Type 2 diabetes, insulin user† (n = 1,370) | 110 | 9,180.05 | 11.98250 | 5.068 (4.198, 6.118) | 3.185 (2.638, 3.846) | 2.420 (1.993, 2.937) |
| P for trend | <0.0001 | <0.0001 | <0.0001 |
| All-cause death | | | | | | |
| No diabetes (n = 348,152) | 14,290 | 2,730,259.00 | 5.23390 | 1 (Ref.) | 1 (Ref.) | 1 (Ref.) |
| Type 2 diabetes, insulin non-user† (n = 14,397) | 1,226 | 110,508.11 | 11.09420 | 2.121 (2.000, 2.248) | 1.257 (1.185, 1.332) | 1.135 (1.067, 1.206) |
| Type 2 diabetes, insulin user† (n = 1,370) | 318 | 9,498.35 | 33.47950 | 6.409 (5.735, 7.162) | 3.620 (3.239, 4.046) | 3.037 (2.706, 3.407) |
| P for trend | <0.0001 | <0.0001 | <0.0001 |

*Adjusted for age, sex, monthly income, and Charlson Comorbidity Index. †Only those with diabetes duration of <5 years were included among people with type 2 diabetes. Bold indicates statistically significant values among the hazard ratios.
during follow-up among people with type 2 diabetes. However, such studies had the following limitations which restricted the application of their results to the general type 2 diabetes population. Although Smooke et al.9 and Anselmino et al.10 reported increased premature all-cause mortality associated with insulin-treated diabetes, they limited the study population to patients with advanced systolic heart failure referred to a single center9, or to patients with established coronary artery disease10. Furthermore, the type of diabetes (type 1 vs type 2) was not discriminatively described9,10, and the duration of diabetes was not presented10 or was markedly varied between the insulin-treated and non-insulin-treated groups9. In a retrospective cohort study, Currie et al.11 compared the risk of adverse outcomes, including the first major adverse cardiac event and all-cause mortality during follow-up in people with type 2 diabetes treated with five different regimens: metformin alone, sulfonylurea alone, insulin alone, a metformin plus sulfonylurea combination regimen, and an insulin plus metformin combination regimen. In their analyses11, insulin monotherapy was associated with higher hazards for major adverse cardiac events and all-cause mortality during follow-up compared to the metformin monotherapy, and the hazard of all-cause mortality during follow-up was higher for insulin monotherapy vs all other regimens. However, prescriptions for people with type 2 diabetes in their study were restricted to only five regimens consisting of metformin, sulfonylurea, insulin monotherapy, and sulfonylurea or insulin combined with metformin, and the implication of overall requirement for insulin treatment in type 2 diabetes as a predictor of adverse outcomes was not fully explored. In an analysis including 8,192 overweight individuals with type 2 diabetes at high risk of cardiovascular disease from the Sibutramine Cardiovascular Outcomes (SCOUT) trial29, insulin monotherapy was associated with a higher risk of cardiovascular events than metformin monotherapy or diet-only treatment. However, analysis of risks associated with overall use of insulin compared with no insulin use in the same study29 showed neutral effects on cardiovascular events.

Considering that previous RCTs demonstrated no significant increase in cardiovascular outcomes and early mortality associated with insulin treatment itself6,7, the higher hazards of cardiovascular disease and all-cause mortality during follow-up among people with insulin-treated type 2 diabetes compared to people with non-insulin-treated type 2 diabetes in the current study may originate from the following factors rather than the effect of insulin itself. First, differences in glycemic control states possibly due to variations in insulin resistance and/or residual beta-cell function may have affected the results, although this could not be determined in this study due to a lack of information. Since diabetes is a progressive disease with a wide spectrum, physicians in the real-world will prescribe treatment regimens reflecting this progression and disease control states in each patient, especially for type 2 diabetes11. For example, people with type 2 diabetes who are effectively controlled with lifestyle modification only or one or two oral medications will remain on these treatments, whereas those who develop severe hyperglycemia or complications and those who

| Group                        | Events (n) | Follow-up duration (person-years) | Incidence rate (per 1000 person-years) | Unadjusted    | Age and sex-adjusted | Multivariable adjusted* |
|------------------------------|-----------|-----------------------------------|---------------------------------------|--------------|----------------------|-------------------------|
| **Myocardial infarction**    |           |                                   |                                       |              |                      |                         |
| Type 2 diabetes, insulin non-user† | 445       | 109,030.08                        | 4.08144                               | 1 (Ref.)     | 1 (Ref.)             | 1 (Ref.)                |
| (n = 14,397)                 |           |                                   |                                       |              |                      |                         |
| Type 2 diabetes, insulin user†| 81        | 9,247.07                          | 8.75953                               | 2.141 (1.690, 2.713) 2.123 (1.675, 2.690) 1.914 (1.502, 2.441) |
| (n = 1,370)                  |           |                                   |                                       |              |                      |                         |
| P-value                      |           | <0.0001                           | <0.0001                               | <0.0001      |                      |                         |
| **Stroke**                   |           |                                   |                                       |              |                      |                         |
| Type 2 diabetes, insulin non-user† | 673       | 108,423.56                        | 6.20710                               | 1 (Ref.)     | 1 (Ref.)             | 1 (Ref.)                |
| (n = 14,397)                 |           |                                   |                                       |              |                      |                         |
| Type 2 diabetes, insulin user†| 110       | 9,180.05                          | 11.98250                              | 1.926 (1.575, 2.357) 1.89 (1.545, 2.312) 1.676 (1.363, 2.060) |
| (n = 1,370)                  |           |                                   |                                       |              |                      |                         |
| P-value                      |           | <0.0001                           | <0.0001                               | <0.0001      |                      |                         |
| **All-cause death**          |           |                                   |                                       |              |                      |                         |
| Type 2 diabetes, insulin non-user† | 1,226     | 110,508.11                        | 11.09420                              | 1 (Ref.)     | 1 (Ref.)             | 1 (Ref.)                |
| (n = 14,397)                 |           |                                   |                                       |              |                      |                         |
| Type 2 diabetes, insulin user†| 318       | 9,498.35                          | 33.47950                              | 3.020 (2.670, 3.417) 2.906 (2.569, 3.288) 2.535 (2.232, 2.880) |
| (n = 1,370)                  |           |                                   |                                       |              |                      |                         |
| P-value                      |           | <0.0001                           | <0.0001                               | <0.0001      |                      |                         |

*Adjusted for age, sex, monthly income, and Charlson Comorbidity Index. †Only those with diabetes duration of <5 years were included among people with type 2 diabetes. Bold indicates statistically significant values among the hazard ratios.
Glycemic variability in diabetes has emerged as an important factor in predicting adverse outcomes including cardiovascular events and early all-cause mortality. Glycemic variability has been associated with plaque vulnerability and subclinical coronary atherosclerosis. Glycemic variability in type 2 diabetes is closely correlated with the loss of beta-cell function, which might be associated with the requirement for insulin treatment. Therefore, individuals with insulin-treated type 2 diabetes might have had greater glycemic variability, although our dataset does not include this information. Third, more frequent hypoglycemic episodes among people with insulin-treated type 2 diabetes than among those with non-insulin-treated type 2 diabetes may have affected our findings. According to an analysis of 828 day-patient glycemic profiles from people with both types of diabetes (T1D, insulin-treated type 2 diabetes, and non-insulin-treated type 2 diabetes) hypoglycemic episodes were second most frequent in people with insulin-treated type 2 diabetes and least frequent in those with non-insulin-treated type 2 diabetes. Severe hypoglycemia has been closely related to the risk of cardiovascular events and early all-cause mortality in populations with both types of diabetes through the effect of low blood glucose itself or activated sympathoadrenal response, promotion of inflammatory and pro-thrombotic status, and alterations in hemodynamics, electrophysiology, and myocardial perfusion. Lastly, confounding by underlying conditions which affect the requirement for insulin treatment may have influenced the results despite the adjustment for CCI. For instance, the prevalence of ESRD was higher in individuals with insulin-treated type 2 diabetes than in those with non-insulin-treated type 2 diabetes.

Several limitations of our study should be acknowledged. First, due to the study design, clarification of causal relationships and underlying mechanisms is inevitably limited. Second, because only Koreans were included in this study, extrapolation of our findings to different ethnic populations should be conducted with caution. Third, the type 2 diabetes patients included in this study were restricted to individuals that were recently diagnosed (type 2 diabetes for <5 years). However, additional analyses including only individuals either without diabetes or with longer-standing type 2 diabetes (type 2 diabetes for ≥5 years) demonstrated consistent findings (Table S1). Fourth, considering the nature of an observational study, which is subject to potential confounding, unmeasured confounders might have affected the findings, despite our maximal efforts to adjust for measured potential confounders. For example, measures of glycemic control status including glycated hemoglobin were not collected. In addition, higher prevalence of underlying comorbidities including renal insufficiency in individuals with insulin-treated type 2 diabetes, which makes the use of oral diabetic medications difficult, may have affected the findings. However, the main objective of our study was not to evaluate the effect of insulin itself in a well-controlled setting. Rather, we aimed to explore the varied risk profiles for cardiovascular diseases and all-cause mortality during follow-up in the real-world according to the presence of type 2 diabetes and insulin treatment determined by clinicians in real practice. Despite these limitations, our study has major strengths. We used a validated nationwide cohort database, provided by the Korean government, representing the Korean population, and reflecting the real-world practice in Korea. No participants were excluded for having any missing values on at least one variable.

In summary, in this nationwide, population-based real-world cohort study that included 363,919 Korean adults, individuals with recently diagnosed type 2 diabetes exhibited higher hazards for incident MI, stroke, and all-cause mortality during follow-up than those without diabetes, and among individuals with recently diagnosed type 2 diabetes, insulin-treated patients demonstrated an additional increase in the hazards of these adverse outcomes. This excess hazard of adverse outcomes in insulin users might have originated from unfavorable features of this population in the sense of comorbidities, insulin resistance and/or residual beta-cell function, and subsequent glycemic variability and increased hypoglycemic events. The increased hazards of cardiovascular disease and all-cause mortality during follow-up in people with diabetes, particularly insulin-treated diabetes, as demonstrated in this study, represent a substantial burden on society through the loss of labor force participation and productivity. Therefore, our findings advance the argument that close monitoring for cardiovascular risks and cardio-protective interventions should be intensified for Korean adults with diabetes, especially those with insulin-treated diabetes.

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DISCLOSURE
The authors declare no conflicts of interest.
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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** | Hazard ratios and 95% confidence intervals for the incidence of myocardial infarction, stroke, and all-cause death according to the presence of diabetes and insulin use among individuals either without diabetes or with longer-standing type 2 diabetes (diabetes for ≥5 years).