Trends of severe hypoglycemia in patients with type 2 diabetes in Korea: A longitudinal nationwide cohort study

Jae-Seung Yun¹, Kyungdo Han²†, Seung-Hyun Ko¹*†

¹Department of Internal Medicine, College of Medicine, St. Vincent’s Hospital, The Catholic University of Korea, Seoul, Korea, and ²Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea

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*Correspondence
Seung-Hyun Ko
Tel: 82-31-881-8900
Fax: 82-31-253-8898
E-mail address: kosh@catholic.ac.kr

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INTRODUCTION
Severe hypoglycemia (SH) is an advanced and life-threatening form of hypoglycemia that can cause loss of consciousness and cardiovascular disease1,2, and has a negative impact on health-related quality of life with increased costs3,4. The frequencies of SH in diabetes patients substantially vary across studies. A systematic review of 46 population-based studies estimated that the prevalence of SH was 6%, with an incidence rate (IR) of 0.80 per person-years (PYs) in type 2 diabetes patients5. According to a cohort study from OptumLabs Data Warehouse in the USA, there were 9.1 SH visits per 1,000 PYs6. Claims data from privately insured and Medicare Advantage patients with type 2 diabetes reported that the overall rate of SH remained constant (1.3 per 100 PYs) from 2006 to 2013 in the USA7.

Clinical practice for diabetes care, the introduction of new antihyperglycemic agents, and trends in prescription patterns changed remarkably around 2010 and over the past decades. In the present study, we aimed to investigate the trends in the prevalence and incidence of SH in Korean adults with type 2 diabetes between 2002 and 2019. The clinical characteristics of the patients with and without SH occurrence in 2002 and 2019 were also further compared.

MATERIALS AND METHODS
We used the Korean National Health Insurance Service claim database8. In this analysis, we included individuals with type 2 diabetes aged ≥30 years from 1 January 2002 to 31 December 2019. To estimate the trends in the prevalence and IR of SH in type 2 diabetes, we analyzed the total number of patients who visited the emergency department with SH episodes among type 2 diabetes patients. To investigate the temporal changes in SH development, we collected data on all episodes reporting SH as the primary outcome, which was defined as the diagnostic clinical codes for hypoglycemia (ICD-10 codes of E160-162, E1163, E1463)2. We further analyzed the information on the prescription patterns of antihyperglycemic agents and a prior history of SH within 3 years before the current SH events in 2002 and 2019. Data on antihyperglycemic agents (insulin, metformin, sulfonylurea, meglitinide, α-glucosidase inhibitors, thiazolidinedione, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium–glucose cotransporter 2 [SGLT-2] inhibitors) were included. Type 2 diabetes was defined based on the diagnostic ICD-10 codes (E11-E14) and/or the claims for prescriptions of

These authors contributed equally.
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antidiabetic medications. Hypertension was defined as diagnostic ICD-10 codes (I10-I13 or I15) and at least one claim per year for antihypertensive medications. Dyslipidemia was defined as a diagnostic code (E78) and at least one claim per year for a lipid-lowering agent.29

The baseline characteristics are presented as numbers and percentages for categorical variables, and means ± standard deviations for continuous variables. Analyses for the comparison of the baseline characteristics were carried out using independent t-tests for continuous variables, and χ²-tests for categorical variables. We additionally carried out a multiple

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Figure 1 | The trends of (a) severe hypoglycemia (SH) prevalence and incidence, and (b) total number experiencing severe hypoglycemia in Korean adults with type 2 diabetes from 2002 to 2019. The annual incidence rate (IR) of severe hypoglycemia is presented as the number of events per 1,000 person-years.

Figure 2 | The trends of severe hypoglycemia prevalence according to (a) age group and (b) sex in Korean adults with type 2 diabetes from 2002 to 2019.
Table 1 | Clinical characteristics of severe hypoglycemia in type 2 diabetes patients in 2002, 2009 and 2019

|                | 2002       |        |        | 2009       |        |        | 2019       |        |        |
|----------------|------------|--------|--------|------------|--------|--------|------------|--------|--------|
|                | SH (−)     | SH (+) | P-value| SH (−)     | SH (+) | P-value| SH (−)     | SH (+) | P-value|
| n              | 940,198    | 2,758  |        | 2,162,667  | 17,521 |        | 3,926,874  | 23,547 |        |
| Age (years)    |            |        |        |            |        |        |            |        |        |
| 30–39          | 480,052    | 51 (11)| <0.001 | 71,547     | 331 (3.1)| <0.001 | 102,596    | 621 (6.1)| <0.001 |
| 40–49          | 160,286    | 18 (1.1)|        | 293,000    | 10,17 (58)|        | 373,420    | 85 (50)|        |
| 50–59          | 248,842    | 265 (15.3)|        | 556,869    | 2,133 (12.2)|        | 912,918    | 233 (11.6)|        |
| 60–69          | 31,160     | 33 (3.1)|        | 630,425    | 4,139 (23.6)|        | 1,162,173  | 453 (19.3)|        |
| 70–79          | 143,422    | 15.2  |        | 478,812    | 6,680 (38.1)|        | 919,886    | 762 (32.4)|        |
| ≥80            | 28,270     | 301 (10.3)|        | 128,962    | 3,204 (18.3)|        | 455,881    | 739 (31.4)|        |
| Sex (male)     | 476,051    | 56 (10)|        | 1,144,232  | 8,342 (47.6)| <0.0001 | 2,188,623  | 11,747 (49.9)| <0.0001 |
| Hypertension (yes) | 44,399     | 472 (6.7)| <0.001 | 1,405,957  | 14,260 (81.4)| <0.001 | 2,534,352  | 18,967 (80.6)| <0.001 |
| Dyslipidemia (yes) | 153,321   | 163 (19.2)| <0.001 | 872,499    | 6,995 (39.9)| 0.259  | 2,794,104  | 15,944 (67.7)| <0.001 |
| Insulin use    | 129,271    | 138 (45.0)| <0.001 | 251,481    | 5,666 (32.3)| <0.0001 | 361,526    | 7,981 (33.9)| <0.0001 |
| Basal          | 88,093     | 61.1  |        | 197,512    | 4,494 (79.3)|        | 228,418    | 4,957 (62.1)| <0.0001 |
| Pre-meal       | 9,120      | 705 (960)| <0.0001 | 46,185     | 1,133 (20.0)|        | 105,178    | 2,730 (34.2)| <0.0001 |
| Pre-mixed      | 13,322     | 103.3 |        | 46,854     | 1,218 (21.5)|        | 47,412     | 1,421 (17.8)| <0.0001 |
| Oral hypoglycemic agents |        |        |        |            |        |        |            |        |        |
| 01             | 79,788     | 84 (30.2)| <0.001 | 132,816    | 3,174 (18.1)| <0.0001 | 117,852    | 3,198 (13.6)| <0.0001 |
| 1 class        | 50,025     | 532 (3.9)|        | 83,469     | 5,083 (30.0)|        | 1,094,483  | 4,73 (20.1)|        |
| 2 classes      | 304,295    | 324 (7.5)|        | 94,353     | 6,585 (37.6)|        | 1,657,180  | 8,486 (60.0)|        |
| 3 classes      | 558,568    | 594 (48.8)|        | 260,691    | 2,679 (15.3)|        | 1,057,359  | 713 (30.3)|        |
| Sulfonylurea    | 7,635,81    | 61,3 (60.0)| <0.001 | 1,516,201  | 11,52 (65.8)| <0.0001 | 1,393,724  | 12,59 (53.5)| <0.0001 |
| Metformin       | 334,143    | 35.5  |        | 1,332,065  | 8,61 (49.2)| <0.0001 | 3,110,902  | 14,49 (61.6)| <0.0001 |
| Meglitinides    | 299        | 0.32  |        | 73,710     | 868 (50)| <0.0001 | 9,879      | 204 (9.9)|        |
| a-Glucosidase inhibitor | 141,977  | 15.1 (16.6)| 0.024 | 368,900    | 4,005 (22.9)| <0.0001 | 50,353     | 753 (3.2)|        |
| Thiazolidinedione| 34,257   | 36.4  |        | 185,753    | 1,238 (7.1)| <0.0001 | 339,460    | 2,308 (9.8)| <0.0001 |
| DPP-4 inhibitor | –         | –     |        | 33,762     | 113 (6.6)| <0.0001 | 2,225,267  | 12,39 (52.6)| <0.0001 |
| SGLT-2 inhibitor | –         | –     |        | –         | –     |        | 283,798    | 688 (2.9)| <0.0001 |
| No insulin/no SU | 76,563   | 83.6  |        | 456,177    | 1,581 (9.02)| <0.0001 | 2,934,86 (74.7)| 13,794 (58.6)| <0.0001 |
| Duration of DM medication (years) | –       | –     | <0.001 | 40 ± 2.6   | 49 ± 2.4| <0.0001 | 8.1 ± 5.8  | 12.1 ± 5.4| <0.0001 |
| SH in previous 3 years | –       | –     | <0.001 | 23,677     | 2,639 (15.1)| <0.0001 | 419,93 (49.4)| 409 (74.4)| <0.0001 |
| SH event number in previous 3 years | –       | –     | <0.001 | 2,138,990  | 14,882 (84.9)| <0.0001 | 3,884,938  | 19,45 (82.6)| <0.0001 |

Data are n (%) or mean ± standard deviation. DM, diabetes; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium–glucose cotransporter 2; SH, severe hypoglycemia; SU, sulfonylurea. *P-value for 2009 versus 2019. †0 means insulin monotherapy.
logistic regression analysis between the groups with and without SH. A two-sided P-value of <0.05 was considered significant. All statistical analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS
The trends of SH prevalence and incidence in Korean adults with type 2 diabetes are shown in Figure 1. The number of all adults diagnosed with type 2 diabetes was 942,956 in 2002 and 3,950,421 in 2019. The prevalence of SH was 0.29% in 2002 and 0.60% in 2019. It steadily increased from 2002 to 2012 (0.87%), and then gradually decreased until 2019 (Figure 1a). The IR increased between 2003 (3.56/1,000 PYs) and 2012 (6.84/1,000 PYs), and then, the trend has gradually declined since 2012. The IR for SH was 4.43/1,000 people in 2019 (Figure 1a). Although the prevalence and IRs showed decreasing tendencies, the absolute number of patients experiencing SH has been steadily increasing. This increase seems to result from an increase in the total population of people with type 2 diabetes and a growing portion of the aging population. Approximately 23,000 cases of SH occur every year among type 2 diabetes patients in Korea. (Figure 1b). The prevalence increased rapidly with age and was remarkably higher in adults aged ≥70 years. In 2019, the prevalence of SH in patients aged in their 30s, 40s, 50s, 60s and 70s, and those aged ≥80 years was 0.30%, 0.25%, 0.30%, 0.39%, 0.82%, and 1.60%, respectively (Figure 2a). A total of 63.8% of total SH cases occurred in people aged ≥70 years in 2019. Severe hypoglycemia was more prevalent in women than men throughout the study period (women vs men, 0.30% vs 0.28% in 2002, and 0.67% vs 0.53% in 2019, respectively; Figure 2b).

We analyzed the changes in the characteristics of people with type 2 diabetes who experienced SH over the past 10 years by comparing the data from 2002 and 2019. The trends in the utilization of antihyperglycemic agents have changed dramatically among type 2 diabetes patients in Korea. The proportion of people with SH receiving sulfonylurea was 65.8% in 2009 and 53.5% in 2019 (P < 0.001). However, the proportion of insulin users in the population with SH events was not significantly different between 2009 and 2019 (32.3% vs 33.9%, P = 0.117). The proportions of people with type 2 diabetes receiving meglitinide or α-glucosidase inhibitor decreased significantly; however, the proportions of patients receiving metformin, DPP-4 inhibitors and SGLT-2 inhibitors remarkably increased from

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Table 2 | Multiple logistic regression analysis between the groups with and without severe hypoglycemia

| Odds ratio (all adjusted) | 2002 | P-value | 2009 | P-value | 2019 | P-value |
|---------------------------|------|---------|------|---------|------|---------|
| Age (years)               |      |         |      |         |      |         |
| 30–39                     | 1 (ref) | <0.0001 | 1 (ref) | <0.0001 | 1 (ref) | <0.0001 |
| 40–49                     | 0.763 (0.591, 0.984) | 0.711 (0.628, 0.805) | 0.874 (0.768, 0.995) |      |         |         |
| 50–59                     | 0.808 (0.636, 1.026) | 0.699 (0.522, 0.874) | 0.895 (0.794, 1.008) |      |         |         |
| 60–69                     | 1.236 (0.983, 1.556) | 1.007 (0.9, 1.127) | 0.963 (0.856, 1.082) |      |         |         |
| 70–79                     | 1.929 (1.527, 2.439) | 1.763 (1.576, 1.972) | 1.428 (1.270, 1.605) |      |         |         |
| 80                        | 3.015 (2.337, 3.89) | 2.614 (2.327, 2.936) | 1.935 (1.719, 2.179) |      |         |         |
| Sex (female)              | 0.965 (0.893, 1.043) | 0.993 (0.962, 1.025) | 0.6839 | 1.051 (1.022, 1.080) | 0.0004 |
| Hypertension              | 1.524 (1.395, 1.665) | 1.482 (1.423, 1.543) | 0.0001 | 1.295 (1.251, 1.340) | <0.0001 |
| Dyslipidemia              | 0.967 (0.876, 1.068) | 0.947 (0.917, 0.978) | 0.0009 | 0.908 (0.881, 0.935) | <0.0001 |
| Insulin use               | 2.96 (2.629, 3.332) | 2.641 (2.519, 2.768) | 0.0001 | 1.729 (1.668, 1.793) | <0.0001 |
| Oral hypoglycemic agents  |      |         |      |         |      |         |
| 0                         | 1 (ref) | 0.004 | 1 (ref) | <0.0001 | 1 (ref) | <0.0001 |
| 1 class                   | 2.491 (0.345, 17.994) | 0.88 (0.691, 1.119) | 0.617 (0.485, 0.785) |      |         |         |
| 2 classes                 | 9.259 (0.179, 47.975) | 1.376 (0.859, 2.204) | 0.559 (0.347, 0.901) |      |         |         |
| ≥3 classes                | – | 2.103 (1.033, 4.281) | 0.508 (0.246, 1.048) |      |         |         |
| Sulfonylurea              | 0.339 (0.047, 2.44) | 0.2825 | 1.201 (0.948, 1.521) | 0.1293 | 1.940 (1.526, 2.467) | <0.0001 |
| Metformin                 | 0.272 (0.038, 1.957) | 0.1957 | 0.769 (0.607, 0.974) | 0.0296 | 0.687 (0.541, 0.874) | 0.0022 |
| Thiazolidinedione         | 0.417 (0.058, 29.83) | 0.3835 | 0.955 (0.754, 1.269) | 0.6998 | 1.578 (1.244, 2.003) | 0.0002 |
| DPP-4 inhibitors          | – | – | 0.663 (0.493, 0.89) | 0.0062 | 1.155 (0.909, 1.468) | 0.2385 |
| α-Glucosidase inhibitors | 0.388 (0.054, 2.797) | 0.3475 | 1.002 (0.79, 1.27) | 0.9875 | 1.965 (1.528, 2.526) | <0.0001 |
| SGLT-2 inhibitors         | – | – | – | 0.783 (0.611, 1.004) | 0.0543 |
| Previous SH history       | – | – | 7.607 (7.262, 7.969) | <0.0001 | 8.470 (8.155, 8.798) | <0.0001 |

Adjusted for age, sex, presence of hypertension or dyslipidemia, insulin use, classes of antihyperglycemic agents, use of sulfonylurea, metformin, thiazolidinedione, dipeptidyl peptidase-4 inhibitors (DPP-4), α-glucosidase inhibitors or sodium–glucose cotransporter 2 (SGLT-2) inhibitors, and presence or history of severe hypoglycemia (SH) within the past 3 years.
2009 to 2019 (P for all <0.001). Compared with patients without SH events, the patients with SH events showed higher use of insulin and meglitinide, longer durations of diabetes treatment, use of multiple oral hypoglycemic agents, and lower use of metformin, DPP-4 inhibitors and SGLT-2 inhibitors (P for all <0.001). In particular, 15–17% of patients with SH experienced at least one event of antecedent SH within the preceding 3 years (Table 1). Multiple logistic regression analysis showed that older age, insulin or SU use and previous SH history were significantly associated with SH (Table 2).

DISCUSSION
From the present study, we found that the prevalence and incidence of SH decreased gradually from 2012 in type 2 diabetes patients. However, the absolute frequency of SH remains largely unchanged and steadily increases despite several efforts to reduce SH, because the diabetes population has increased. As large-scale intensive glucose control studies have shown at least a two- to threefold increased risk of SH compared with standard treatment groups, many clinical practice guidelines have recommended active avoidance of hypoglycemia or SH. DPP-4 inhibitors were introduced and began to be prescribed from 2008 to 2010 in Korea. Therefore, the reduction in the incidence of SH seems to most likely be due to the increased prescription rate of antihyperglycemic medications without hypoglycemia risk, such as DPP-4 inhibitors or SGLT-2 inhibitors, less strict treatment goals, the individualization of diabetes therapy according to clinical practice guidelines and active diabetes education for preventing hypoglycemia.

The strength of the present study was that it was a large-scale nationwide study with long-term follow up in type 2 diabetes patients. At the same time, our study lacked important variables for glycemic control status, medication dosages and detailed information about disease duration. Despite these limitations, it is very important to know the current situation of SH occurrence, because there are still a considerable number of patients suffering from SH, and it could induce very serious clinical outcomes, especially in patients who are very old, fragile, and have long-standing diabetes and multiple underlying advanced comorbidities. In addition to comprehensive diabetes care, a more intensive, individualized and patient-centered detailed approach with education for the prevention of SH should be emphasized in this high-risk population of type 2 diabetes patients.

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DISCLOSURE
The authors declare no conflict of interest.

Approval of the research protocol: Approved by both the Korean National Health Insurance Service and the Institutional Review Board of the Catholic University of Korea (XC19WIDI0105).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

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REFERENCES
1. Choi SY, Ko SH. Severe hypoglycemia as a preventable risk factor for cardiovascular disease in patients with type 2 diabetes mellitus. Korean J Intern Med 2021; 36: 263–270.
2. Yun J-S, Park Y-M, Han K, et al. Severe hypoglycemia and the risk of cardiovascular disease and mortality in type 2 diabetes: a nationwide population-based cohort study. Cardiovasc Diabetol 2019; 18: 103.
3. Rhee SY, Hong SM, Chon S, et al. Hypoglycemia and medical expenses in patients with type 2 diabetes mellitus: an analysis based on the Korea National Diabetes Program Cohort. PLoS One 2016; 11: e0148630.
4. Li S, Fang LJ, Lee A, et al. The association between diabetes-related distress and fear of hypoglycaemia in patients with type 2 diabetes mellitus: a cross-sectional descriptive study. Nurs Open 2021; 8: 1668–1677.
5. Edridge CL, Dunkley AJ, Bodicoat DH, et al. Prevalence and incidence of hypoglycaemia in 532,542 people with type 2 diabetes on oral therapies and insulin: a systematic review and meta-analysis of population based studies. PLoS One 2015; 10: e0126427.
6. McCoy RG, Lipska KJ, Van Houten HK, et al. Association of cumulative multimorbidity, glycemic control, and medication use with hypoglycemia-related emergency department visits and hospitalizations among adults with diabetes. JAMA Netw Open 2020; 3: e1919099.
7. Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006–2013. Diabetes Care 2017; 40: 468–475.
8. Kim HK, Song SQ, Noh J, et al. Data configuration and publication trends for the Korean National Health Insurance and Health Insurance review & assessment database. Diabetes Metab J 2020; 44: 671–678.
9. Kim Y-S, Park Y-M, Han K-D, et al. Fasting glucose level and all-cause or cause-specific mortality in Korean adults: a nationwide cohort study. Korean J Intern Med 2021; 36: 647–658.
10. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. Diabetes Care 2021; 44(Suppl 1): S111–S124.
11. Hur KY, Moon MK, Park JS, et al. Clinical practice guidelines for diabetes mellitus of the Korean Diabetes Association. Diabetes Metab J 2021; 2021: 461–481.
12. Tian J, Ohkurna T, Cooper M, et al. Effects of intensive glycemic control on clinical outcomes among patients with type 2 diabetes with different levels of cardiovascular risk and hemoglobin A1c in the ADVANCE trial. Diabetes Care 2020; 43: 1293–1299.
13. Davis SN, Duckworth W, Emanuele N, et al. Effects of severe hypoglycemia on cardiovascular outcomes and death in the veterans affairs diabetes trial. *Diabetes Care* 2019; 42: 157–163.

14. Kamalinia S, Josse RG, Donio PJ, et al. Risk of any hypoglycaemia with newer antihyperglycaemic agents in patients with type 2 diabetes: a systematic review and meta-analysis. *Endocrinol Diabetes Metab* 2019; 3: e00100.

15. Davis TME, Bruce DG, Finn J, et al. Temporal changes in the incidence and predictors of severe hypoglycaemia in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Obes Metab* 2019; 21: 648–657.

16. Kong APS, Yang X, Luk A, et al. Severe hypoglycemia identifies vulnerable patients with type 2 diabetes at risk for premature death and all-site cancer: the Hong Kong diabetes registry. *Diabetes Care* 2014; 37: 1024–1031.

17. Misra-Hebert AD, Pantalone KM, Ji X, et al. Patient characteristics associated with severe hypoglycemia in a type 2 diabetes cohort in a large, integrated health care system from 2006 to 2015. *Diabetes Care* 2018; 41: 1164–1171.