Long-term clinical outcomes of oral antidiabetic drugs as fixed-dose combinations: A nationwide retrospective cohort study

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Abstract
Aim: To compare treatment patterns and clinical outcomes of single-pill fixed-dose combination (FDC) and two-pill combination (TPC) therapies using real-world data.

Methods: We conducted a nationwide retrospective cohort study using South Korea’s healthcare database (2002-2015). We identified two cohorts of incident patients with type 2 diabetes who initiated FDC or TPC therapy within 4 months of their first prescription for metformin or sulphonylurea. We examined persistence and adherence patterns and the clinical outcome of a composite endpoint of death or hospitalization for acute myocardial infarction, heart failure or stroke and compared the differences in treatment patterns and clinical outcomes using Cox models.

Results: Of 5143 and 10 973 patients who initiated FDC and TPC therapy, respectively, we identified 5143 patient pairs after propensity score matching. The FDC group exhibited greater median time to treatment discontinuation (163 vs. 146 days), and proportion of days covered at 12 months (mean 0.60 vs. 0.57, P < .0001) and at 24 months (0.53 vs. 0.51, P = .014) than the TPC group. The FDC group, compared with the TPC group, had reduced risks of the composite clinical outcome (hazard ratio 0.86, 95% confidence intervals 0.77-0.97) and hospitalization for stroke (0.80, 0.67-0.96).

Conclusion: FDC therapy may provide favourable cardiovascular benefits, especially reducing the risk of hospitalization for stroke, and has better medication adherence among patients with type 2 diabetes.

KEYWORDS
adherence, clinical outcome, dipeptidyl peptidase-4 inhibitor, fixed-dose combination, persistence, sulphonylurea, two-pill combination

1 INTRODUCTION

The prevalence of type 2 diabetes has increased at a surprising rate and remains a global health concern.1 Failure to control type 2 diabetes deteriorates quality of life and well-being and compromises related organs in the long term, resulting in morbidity and mortality.2 Owing to the increasing disease burden of diabetes, many pharmaceutical companies have developed fixed-dose combination (FDC)
therapies for metabolic diseases, because they have a lower price than two-pill combination (TPC) therapy and improve medication adherence. However, only a few studies have investigated the long-term clinical outcomes of FDC therapy with antidiabetic medications.

Prior evidence suggests that early FDC medication in the treatment pathway may have more advantages from the perspective of patients and physicians. Improving compliance with oral antidiabetic drugs (OADs) and/or other medications for complications is key to prevent or remedy long-term co-morbidities associated with diabetes and minimize the economic burden. A previous study reported a strong association between adherence and healthcare costs, where a 10% increase in adherence was associated with a 0.1% reduction in HbA1c levels. Furthermore, poor adherence is associated with poor glycaemic control and subsequently increased morbidity, mortality and healthcare costs. To ease the complexity of treatment for type 2 diabetes, FDC may enhance medication adherence and thus glycaemic control by simplifying the treatment regimen for patients with type 2 diabetes. Therefore, there is a clinical need to better elucidate the role of FDCs in patients with type 2 diabetes in routine care by comparing the treatment patterns of adherence and persistence and clinical outcomes versus TPCs using real-world data.

2 | METHODS

2.1 | Data source

This study used the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database of South Korea from 1 January 2002 to 31 December 2015. The NHIS-NSC was established as a research database, representing a 2.2% random sample of the entire Korean population (approximately 50 million people), making it a highly representative cohort. This real-world data source contains a wide range of demographic variables including sex, age, residential area, type of health insurance; socioeconomic variables, such as income rank and disability; vital information, including date of death and cause of death; and diagnosis-related variables, including diagnosis setting, diagnostic code (International Classification of Disease [ICD]-10 classification codes) and drug prescription information (drug name, prescription date and dose). All prescriptions in the NHIS-NSC database are given a domestic National Drug Chemical code based on the Anatomical Therapeutic Chemical classification system of the World Health Organization.

2.2 | Study population

2.2.1 | Base cohort

The base cohort consisted of patients newly prescribed metformin (MET) or sulphonylurea (SU) after their incident diagnosis of type 2 diabetes (ICD-10: E11-E14), with the date of base cohort entry defined as the earliest prescription date of MET or SU. We identified all individuals without a diagnosis of type 2 diabetes from 1 January 2002 to 31 December 2013 (enrolment period) to restrict incident patients with type 2 diabetes. We excluded all individuals with a diagnosis of type 1 diabetes at all times during the study period. Additionally, patients aged younger than 18 years at base cohort entry, prescribed any antidiabetic drugs in the year prior to base cohort entry, hospitalized for transient ischaemic attack, acute myocardial infarction (AMI) or heart failure (HF) in the year prior to base cohort entry, or who visited the emergency department for TIA or stroke in the year prior to base cohort entry, were excluded.

2.2.2 | Study cohort

From the base cohort, we identified patients prescribed (1) MET plus SU (MET+SU) or (2) MET plus dipeptidyl peptidase-4 inhibitor (DPP4i; MET+DPP4i), as either FDC or TPC therapy. The MET+SU cohort was defined as individuals prescribed MET+SU as an FDC or prescribed MET and SU separately (TPC) within 120 days after base cohort entry. The analogous definition was used for the MET+DPP4i cohort with SU replaced by DPP4i. The index date or the date of follow-up was defined as the earliest date of prescription for the FDC or TPC. This definition was in agreement with the recommendations of the Korean Diabetes Association (KDA) and the reimbursement criteria for antidiabetic medications in South Korea (Figure S1).

2.3 | Exposure

Treatment regimens of MET+SU or MET+DPP4i, either as FDC or TPC, comprised more than 70% of total dual OAD prescriptions in South Korea. Because of the reimbursement criteria and concerns regarding insufficient power, we did not investigate other dual OAD combinations (Tables S1 and S2). Indeed, the proportions of MET+DPP4i and MET+SU among the total dual combinations were 50% and 34% in 2015, respectively, according to the KDA annual report.

2.4 | Outcome

The primary outcome of interest was the clinical outcome, defined as a composite endpoint of all causes of death and hospitalization for stroke, AMI or HF. The individual components of the composite outcomes were the secondary clinical outcomes. A previous validation study found overall positive predictive values of 92.0% and 90.5% for AMI and stroke, respectively, in the NHIS-NSC database compared with the hospital’s electronic medical records. For clinical outcomes, patients were followed up from the index date until the earliest of outcome occurrence or end of the study period (31 December 2015), using an intention-to-treat analysis. An as-treated follow-up definition was used in a sensitivity analysis, with patients censored on the
earliest outcome occurrence, treatment discontinuation or end of the study period.

For treatment pattern outcomes, we assessed adherence and persistence at 12 and 24 months using as-treated analysis after the index date. Adherence to FDC or TPC therapy was defined as the proportion of days covered (PDC), which was calculated as the duration of the prescription divided by the duration. Second, persistence of FDC or TPC therapy was defined as the duration between the index date and discontinuation of the medication of interest. Treatment discontinuation was defined as the absence of a refill prescription(s) within 150% of the previous prescription supply (e.g. if the previous prescription supply was for 30 days, the grace period would be 45 days). Moreover, all medications of interest were considered at the class level and not at the individual active ingredient level (e.g. for DPP4is, switching from sitagliptin to saxagliptin would not be considered a discontinuation).

In the sensitivity analysis, we varied the definition of the grace period to investigate the robustness of our study outcomes.

### 2.5 Potential confounders

We assessed the sociodemographic characteristics of sex, age, area of residence, insurance quintile and health insurance type on the index date. The clinical characteristics of the Charlson co-morbidity index (CCI) score, co-morbidities (AMI, stroke, HF, hypertension, hyperlipidaemia, diabetic nephropathy, diabetic retinopathy and diabetic neuropathy) and use of co-medications (antiplatelet, statin, antihypertensive and diuretics) were assessed for the year prior to the index date. Lifestyle variables, such as smoking, alcohol consumption and body mass index, were assessed in the 2-year period prior to the index date, because national health examinations are offered

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**FIGURE 1** Flow chart showing the inclusion and exclusion criteria for the study patients. Abbreviation: AMI, acute myocardial infarction; DPP4i, dipeptidyl peptidase-4 inhibitor; ED, emergency department; FDC, fixed-dose combination; MET, metformin; SU, sulphonylurea; TIA, transient ischaemic attack; TPC, two-pill combination
| Variable                               | Before matching | After matching (c = 0.676) |
|----------------------------------------|-----------------|---------------------------|
|                                        | TPC (n = 10 973) | FDC (n = 5143) | aSD        | TPC (n = 5143) | FDC (n = 5143) | aSD        |
| Follow-up duration, d, mean (SD)       | 414.0 (618.4)   | 417.6 (579.9) |              | 423.1 (615.6) | 417.6 (579.9) |              |
| Sex, n (%)                             |                 |               | 0.007       |               | 0.023          |              |
| Male                                   | 6515            | 59.2          | 3035        | 60.0          | 3035           | 58.9        |
| Female                                 | 4458            | 40.5          | 2108        | 39.8          | 2108           | 40.9        |
| Age at index date, y, mean (SD)        | 54.4 (12.6)     | 53.5 (12.1)   | 0.070       | 53.5 (11.9)   | 53.5 (12.1)    | 0.002       |
| ≤44                                    | 2483            | 22.6          | 1215        | 23.6          | 1215           | 23.6        |
| 45-54                                  | 3306            | 30.0          | 1613        | 31.3          | 1613           | 31.3        |
| 55-64                                  | 2675            | 24.3          | 1338        | 26.0          | 1338           | 26.0        |
| 65-74                                  | 1857            | 16.9          | 760         | 14.7          | 760            | 14.7        |
| ≤75                                    | 652             | 5.9           | 217         | 4.2           | 217            | 4.2         |
| Residence, n (%)                       |                 |               | 0.094       |               | 0.082          |              |
| Urban                                  | 4161            | 37.8          | 2187        | 42.4          | 1979           | 38.4        |
| Rural                                  | 6812            | 61.9          | 2956        | 57.4          | 3164           | 61.4        |
| Insurance quintile*, n (%)             |                 |               | 0.069       |               | 0.069          |              |
| Q1-Q2                                  | 2506            | 22.8          | 1066        | 20.7          | 1096           | 21.3        |
| Q3-Q4                                  | 1592            | 14.5          | 770         | 14.9          | 755            | 14.6        |
| Q5-Q6                                  | 1974            | 17.9          | 888         | 17.2          | 949            | 18.4        |
| Q7-Q8                                  | 2349            | 21.3          | 1102        | 21.4          | 1166           | 22.6        |
| Q9-Q10                                 | 2552            | 23.2          | 1317        | 25.6          | 1177           | 22.8        |
| Insurance type, n (%)                  |                 |               | 0.104       |               | 0.008          |              |
| Employee-insured                       | 5476            | 49.8          | 2772        | 53.8          | 2785           | 54.0        |
| Self-insured                           | 4657            | 42.3          | 2086        | 40.5          | 2082           | 40.4        |
| Medical aid                            | 840             | 7.6           | 285         | 5.5           | 276            | 5.4         |
| Charlson co-morbidity index, mean (SD) | 0.6 (1.1)       | 0.7 (1.2)     | 0.057       | 0.6 (1.2)     | 0.7 (1.2)      | 0.005       |
| 0                                      | 7666            | 69.7          | 3453        | 67.0          | 3471           | 67.3        |
| 1                                      | 1452            | 13.2          | 678         | 13.2          | 689            | 13.4        |
| 2+                                     | 1855            | 16.9          | 1012        | 19.6          | 983            | 19.1        |
| Co-morbidities, n (%)                  |                 |               |             |               |                |              |
| Acute myocardial infarction             | 42              | 0.4           | 22          | 0.4           | 21             | 0.4         |
| Stroke                                 | 223             | 2.0           | 104         | 2.0           | 121            | 2.3         |
| Heart failure                          | 142             | 1.3           | 87          | 1.7           | 83             | 1.6         |
| Hypertension                           | 3049            | 27.7          | 1692        | 32.8          | 1716           | 33.3        |
| Hyperlipidaemia                        | 1443            | 13.1          | 929         | 18.0          | 927            | 18.0        |
| Hypercholesterolaemia                  | 686             | 6.2           | 473         | 9.2           | 446            | 8.7         |
| Hypertriglyceridaemia                  | 59              | 0.5           | 43          | 0.8           | 39             | 0.8         |
| Diabetic nephropathy                   | 0               | 0.0           | 1           | 0.0           | 0              | 0.0         |
| Diabetic retinopathy                   | 98              | 0.9           | 40          | 0.8           | 43             | 0.8         |
| Diabetic neuropathy                    | 1               | 0.0           | 0           | 0.0           | 1              | 0.0         |
| Co-medications, n (%)                  |                 |               |             |               |                |              |
| Antiplatelet                           | 844             | 7.7           | 506         | 9.8           | 450            | 8.7         |
| Statins                                | 739             | 6.7           | 513         | 10.0          | 484            | 9.4         |
| Ezetimibe                              | 21              | 0.2           | 22          | 0.4           | 15             | 0.3         |
| Fibrate                                | 61              | 0.6           | 42          | 0.8           | 41             | 0.8         |
| Antihypertension                       | 2401            | 21.8          | 1354        | 26.3          | 1328           | 25.8        |
| Diuretics                              | 452             | 4.1           | 218         | 4.2           | 245            | 4.8         |
Initially validated algorithms were used to calculate CCI scores.

### Statistical analyses

To minimize any effects from measured confounders and obtain comparability between the FDC and TPC groups, matching (1:1 ratio) was performed based on the propensity score, which was estimated using a multivariable logistic regression model. Balance in baseline covariates was determined using the absolute standardized difference estimate, with a value greater than 0.1 indicating an important imbalance. We used caliper matching, where the maximum tolerated difference was 0.2 of the standard deviation of logit of the propensity score. Moreover, a c-statistic of 0.6-0.8 was considered fit for propensity score matching.

### RESULTS

Of the 195,691 patients newly diagnosed with type 2 diabetes from 2002 to 2015 (base cohort), 10,973 and 5,143 patients initiated TPC

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**TABLE 1** (Continued)

| Variable | Before matching | After matching (c = 0.676) |
|----------|-----------------|---------------------------|
|          | TPC (n = 10,973) | FDC (n = 5,143) | aSD | TPC (n = 5,143) | FDC (n = 5,143) | aSD |
| Fasting blood sugar levels, mean (SD) | 139.2 (44.1) | 135.3 (41.1) | 0.092 | 139.5 (44.4) | 135.3 (41.1) | 0.099 |
| Smoking history, n (%) | | | | | | |
| Yes | 3478 | 31.6 | 1831 | 35.5 | 1806 | 35.0 | 1831 | 35.5 |
| No | 3412 | 31.0 | 1838 | 35.7 | 1851 | 35.9 | 1838 | 35.7 |
| Missing | 4083 | 37.1 | 1474 | 28.6 | 1486 | 28.8 | 1474 | 28.6 |
| Alcohol consumption, n (%) | | | | | | |
| Yes | 3283 | 29.8 | 1726 | 33.5 | 1714 | 33.3 | 1726 | 33.5 |
| No | 3607 | 32.8 | 1943 | 37.7 | 1943 | 37.7 | 1943 | 37.7 |
| Missing | 4083 | 37.1 | 1474 | 28.6 | 1486 | 28.8 | 1474 | 28.6 |
| Body mass index (kg/m²), n (%) | | | | | | |
| <25 | 2640 | 24.0 | 1276 | 24.8 | 1262 | 24.5 | 1276 | 24.8 |
| 25-30 | 3401 | 30.9 | 1835 | 35.6 | 1862 | 36.1 | 1835 | 35.6 |
| ≥30 | 848 | 7.7 | 558 | 10.8 | 533 | 10.3 | 558 | 10.8 |
| Missing | 4084 | 37.1 | 1474 | 28.6 | 1486 | 28.8 | 1474 | 28.6 |

Abbreviations: aSD, absolute standardized difference; FDC, fixed-dose combination; SD, standard deviation; TPC, two-pill combination.

**TABLE 2** Time to treatment discontinuation at 12- and 24-month persistence rate in the propensity score-matched cohort

| Index therapy | Index drug class | N | Median persistence (days, IQR) | HR (95% CI), P value | 12 mo persistence rate (%) | 24 mo persistence rate (%) |
|---------------|-----------------|---|--------------------------------|---------------------|--------------------------|--------------------------|
| All | TPC | 5143 | 146 (41-543) | ref | 32.9 | 20.8 |
| | FDC | 5143 | 163 (46-543) | 0.92 (0.89-0.96), <.0001 | 36.0 | 23.0 |
| MET + DPP4i | TPC | 913 | 277 (63-784) | ref | 47.3 | 31.9 |
| | FDC | 1936 | 204 (61-579) | 1.06 (0.97-1.15), .2301 | 42.7 | 28.4 |
| MET + SU | TPC | 4230 | 121 (37-479) | ref | 30.0 | 18.7 |
| | FDC | 3207 | 139 (44-517) | 0.94 (0.90-0.99), .0154 | 32.5 | 20.6 |

Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitor; FDC, fixed-dose combination; HR, hazard ratio; IQR, interquartile range; MET, metformin; SU, sulphonylurea; TPC, two-pill combination.

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Treatment persistence and subgroup differences were evaluated using Kaplan–Meier plots and log-rank tests, respectively. Moreover, the PDC (measure of adherence) between the FDC and TPC groups was compared using the Wilcoxon signed rank sum test and the mean PDC was compared using Student’s t-test. Multivariable Cox hazard regression models were used to compare persistence (time to discontinuation) and incidence of clinical outcomes between the FDC and TPC groups by estimating the hazard ratio (HR) with 95% confidence intervals (CIs). All statistical analyses were conducted using SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC).

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*b*Insurance quintile was classified into 11 groups ranging from the 0th quintile to the 10th quintile, according to the type of health insurance; the 0th quintile corresponds to the most deprived and the 10th quintile is the most affluent; thus, a higher number indicates higher income.
and FDC therapy, respectively, after 1 January 2003. After propensity score matching, 5143 patient-pairs were identified (Figure 1).

All baseline covariates were well balanced and had an absolute standardized difference of less than 0.1 after propensity score matching. The mean duration of follow-up was also comparable between the FDC group (417.6 days; SD 579.9 days) and TPC group (423.1 days; SD 615.6 days) (Table 1).

The median time to treatment discontinuation was significantly longer in the FDC group (163 days; interquartile range, 46-543 days) than in the TPC group (146 days; interquartile range, 41-543 days) (HR 0.92, 95% CI 0.89-0.96, P < .0001). Moreover, the persistence rates at 12 and 24 months in the FDC group were 36.0% and 23.0%, respectively (Table 2); however, Kaplan-Meier plots revealed no significant difference (Figure S2). Adherence to the medication of interest at 12 and 24 months of follow-up was also greater in the FDC group (mean PDC 0.60 and 0.53 [standard deviation 0.40 and 0.41] at 12 and 24 months, respectively) than in the TPC group (mean PDC 0.63 and 0.57 [standard deviation 0.40 and 0.41] at 12 and 24 months, respectively) (Table 3). Sensitivity analyses for adherence and persistence that varied the length of the grace period and the period for assessing the index medication at (the time, within 60 days, and within 180 days) showed consistent results (Tables S3–S6).

In the propensity score-matched cohort, the FDC group, as compared with the TPC group, had a lower incidence rate of the composite clinical outcome (22.02 vs. 24.57 per 1000 person-years); in the TPC group, the rate was 24.57 per 1000 person-years (HR 0.92, 95% CI 0.89-0.96, P < .0001). The results of additional sensitivity analyses wherein the grace period (50% and 300%) and the period for assessing the index medication were varied (at the time, within 60 days, and within 180 days) also remained consistent (Tables S8 and S9).

The results of our subgroup analyses for the association between the composite clinical outcome and medication regime stratified by select covariates revealed no statistically significant associations (all P values for interaction >.05) (Table S10–S14).

### 4 DISCUSSION

Using South Korea’s comprehensive and nationwide real-world data, we found significantly longer persistence, higher adherence and a lower risk of clinical outcomes associated with patients on FDC therapy versus TPC therapy among patients with type 2 diabetes. Based on the observed higher rates of treatment adherence and persistence associated with FDC and given that adherence to treatment leads to improved glycaemic control among patients with type 2 diabetes, our findings provide additional reasons for healthcare providers to consider FDC therapy over TPC therapy as an optimal treatment strategy for patients with type 2 diabetes with increased baseline cardiovascular risks, especially hospitalization for stroke.

Our findings are generally consistent with those of previous studies that showed a positive association between FDC therapy and adherence and persistence.11,12,21-24 A meta-analysis conducted by Bangalore et al. revealed that FDC therapy improved medication non-compliance by 26% (pooled relative risk, 0.74; 95% CI 0.69-0.80; P < .0001) when compared with a free-drug combination.21 Another study by Barner found 9% improvement in medication adherence, but did not compare it with an active comparator, making it difficult to
| Outcome            | Overall cohort | Matched cohort | Matched cohort |
|--------------------|----------------|----------------|----------------|
|                    | Person-years  | No. of events  | Incidence rate\(^a\) | Crude HR (95% CI) | Adjusted HR (95% CI) | Person-years  | No. of events  | Incidence rate\(^a\) | Crude HR (95% CI) | Adjusted HR (95% CI) |
| Primary outcome    |                |                |                |                |                    |                |                |                |                |                    |
| TPC                | 69 804.4       | 1907           | 27.32          | Reference      | Reference          | 32 272.8       | 793            | 24.57          | Reference      | Reference          |
| FDC                | 23 928.0       | 527            | 22.02          | 0.78 (0.71-0.86) | 0.86 (0.78-0.95)   | 23 928.0       | 527            | 22.02          | 0.89 (0.79-0.99) | 0.86 (0.77-0.97)   |
| Secondary outcome  |                |                |                |                |                    |                |                |                |                |                    |
| Death              |                |                |                |                |                    |                |                |                |                |                    |
| TPC                | 73 509.1       | 1251           | 17.02          | Reference      | Reference          | 33 750.2       | 495            | 14.67          | Reference      | Reference          |
| FDC                | 24 825.0       | 330            | 13.29          | 0.80 (0.71-0.90) | 0.90 (0.80-1.02)   | 24 825.0       | 330            | 13.29          | 0.94 (0.82-1.08) | 0.90 (0.78-1.04)   |
| AMI                |                |                |                |                |                    |                |                |                |                |                    |
| TPC                | 77 736.5       | 171            | 2.20           | Reference      | Reference          | 35 350.8       | 69             | 1.95           | Reference      | Reference          |
| FDC                | 25 725.6       | 58             | 2.25           | 0.96 (0.71-1.30) | 0.98 (0.72-1.32)   | 25 725.6       | 58             | 2.25           | 1.13 (0.79-1.61) | 1.14 (0.80-1.62)   |
| Stroke             |                |                |                |                |                    |                |                |                |                |                    |
| TPC                | 74 791.8       | 719            | 9.61           | Reference      | Reference          | 34 206.8       | 312            | 9.12           | Reference      | Reference          |
| FDC                | 25 115.8       | 192            | 7.64           | 0.73 (0.63-0.86) | 0.81 (0.69-0.95)   | 25 115.8       | 192            | 7.64           | 0.80 (0.67-0.96) | 0.80 (0.67-0.96)   |
| Heart failure      |                |                |                |                |                    |                |                |                |                |                    |
| TPC                | 77 655.0       | 184            | 2.37           | Reference      | Reference          | 35 320.1       | 69             | 1.95           | Reference      | Reference          |
| FDC                | 25 751.9       | 46             | 1.79           | 0.72 (0.52-1.00) | 0.77 (0.55-1.07)   | 25 751.9       | 46             | 1.79           | 0.89 (0.61-1.29) | 0.85 (0.58-1.24)   |

Abbreviations: AMI, acute myocardial infarction; FDC, fixed-dose combination; HR, hazard ratio; TPC, two-pill combination.

\(^a\)Per 1000 person-years.
directly compare with our results.\textsuperscript{22} Although we were able to provide a more accurate estimate of adherence by comparing the FDC with the TPC group, Nishimura et al. reported a much stronger finding than that of our study (>90% vs. 47.5% for the adherent patient rate with PDC ≥0.8 in the FDC group at 12 months).\textsuperscript{12} However, this finding may have resulted from a different definition of the grace period, which was not used in our study. In our sensitivity analysis that varied the grace period, we found an enhanced adherence rate with a PDC of 0.8 or higher at 12 and 24 months under less stringent conditions (Table S5). Although further investigations are warranted on the adherence and persistence of FDC therapy, our findings support the previously reported positive association between FDC therapy and increased adherence and persistence compared with TPC therapy among patients with type 2 diabetes.

Several studies have examined the association between clinical outcomes and FDC and TPC groups, focusing on the improvement of glycaemic control through regime simplification.\textsuperscript{25–28} Although one study showed an association between non-adherence and increased mortality rates, it was probably caused by poor glycaemic control.\textsuperscript{29} Another study that compared drug compliance and morbidities over a 3-year period failed to detect a statistically significant difference in morbidities between TPC and FDC.\textsuperscript{11} Our findings for the composite clinical outcome and hospitalization for stroke associated with FDC versus TPC revealed statistically significant differences in favour of the FDC group. The FDC group had 2.55 and 1.84 fewer events per 1000 person-years, respectively, than the TPC group (Table 4). However, there was no significant difference in mortality rates between the FDC and TPC groups (Figure S3), which is consistent with the findings of a previous study.\textsuperscript{11} Hence, because FDC therapy was associated with a reduced risk of adverse clinical outcomes and improved medication adherence, patients with type 2 diabetes could experience greater clinical benefits with FDC therapy than with TPC therapy.

Our study has several strengths. First, our findings are probably generalizable to the patient population in South Korea and are representative of real-world clinical practice, because we identified our study cohort using a nationwide NHIS-NSC database consisting of large samples of about 1 million people and a well-characterized population based on 14 variables. Second, we identified our study cohort as patients who initiated FDC or TPC therapy within 120 days after their incident diagnosis of type 2 diabetes to restrict the study cohort to patients at similar stages of disease progression.\textsuperscript{30–32} Third, in contrast to previous studies that had a comparatively short follow-up of less than 12 months,\textsuperscript{12,22–24,33–35} we examined the long-term outcomes with a maximum follow-up of 12 years. This is particularly important when investigating treatment patterns in patients with chronic diseases (e.g. type 2 diabetes), because it allows for a better understanding of the long-term benefits versus risks associated with FDC versus TPC therapy. Lastly, our findings suggest that FDC therapy may be a more optimal strategy for patients with type 2 diabetes and could further reduce the cost burden, as such treatments result in a lower reimbursement cost than that for TPC.

Our study has several limitations. First, we were unable to identify the cause of the prominent improvement in hospitalization for stroke associated with FDC versus TPC therapy. Previous meta-analyses of randomized trials and observational studies have shown that tight glycaemic control does not offer any benefit in the prevention of stroke.\textsuperscript{36,37} However, there were significant differences in patient characteristics between the aforementioned studies, which included those prevalent in diabetes and cardiovascular disease, and our study, which included only incident patients with diabetes and cardiovascular diseases. In support of this, our subgroup findings showed a significant reduction in stroke- and heart failure-naive patients receiving FDC medication (Table S10). Considering this, we suggest that FDC medications could contribute to the prevention of hospitalization for stroke among incident patients with diabetes with no prior history of cardiovascular diseases. Second, laboratory or lifestyle variables, such as HbA1c levels, stress and family history of chronic diseases, were unavailable for assessment from the NHIS-NSC database. However, we adopted a new user design, performed several sensitivity analyses, and had consistent results, which are suggestive of minimal residual confounding from such unmeasured covariates. Third, presented data of type 2 diabetes could not fully include recent OADs. For instance, of the nine DPP4i molecules currently marketed and reimbursed in South Korea as of November 2021, we were able to include mainly vildagliptin and sitagliptin at the time of study cohort entry, because the other DPP4i drugs were either yet to be approved or recently launched and introduced into the South Korean market in December 2013. Moreover, it was not until September 2014 when sodium-glucose co-transporter-2 inhibitors were reimbursed in South Korea. Hence, future studies with more recent real-world data, including sodium-glucose co-transporter-2 inhibitors, are needed. Fourth, we measured adherence using the PDC based on the medication dispensed and assumed that medications were taken exactly as prescribed. Although this is not a direct measure of medication adherence, it is considered appropriate when using secondary databases.\textsuperscript{38} Lastly, this was not a randomized study. Observational studies are usually associated with measurable and unmeasurable confounding potentials. Despite the use of multiple methodological approaches to mitigate confounding variables such as propensity score matching and subgroup analysis for measurable confounding, and active comparator and sensitivity analysis for unmeasurable confounding, residual confounding is possible owing to the nature of observational studies. Therefore, we calculated the E-value,\textsuperscript{39} which indicated that our effect estimates were probable to be directed toward the null only when there was a very strong unmeasured confounder (Table S15).

This nationwide retrospective cohort study using real-world data representative of South Korea provided important real-world evidence suggesting that FDC therapy, compared with TPC therapy, could significantly reduce the risk of long-term clinical outcomes, especially hospitalization for stroke, accompanied by higher medication adherence and treatment persistence among patients with type 2 diabetes.

**AUTHOR CONTRIBUTIONS**

S-JC and J-YH conceptualized and designed the study. S-JC, I-SO, HEJ, YMC, YH, OHYY and J-YH analysed and interpreted data and contributed to the writing of the manuscript. HEJ, YMC, YH, OHYY...
and J-YS contributed to the critical revision of the manuscript for important intellectual content. I-SO acquired data and performed the statistical analysis. J-YS supervised the study and had final responsibility for the decision to submit for publication. J-YS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14792.

ETHICS APPROVAL

The present study was approved by the Institutional Review Board of Sungkyunkwan University (No: SKKU-IRB-2020-10-003). The board waived the requirement for informed consent.

AVAILABILITY OF DATA AND MATERIALS

Data generated and/or analysed during the current study cannot be shared publicly because of the data-sharing policy of the National Health Insurance Service (NHIS) of Korea, governed by Article 18 of the Personal Information Protection Act (‘Limitation to Out-of-Purpose Use and Provision of Personal Information’ available at https://elaw.kiri.re.kr/kor_service/lawView.do?hseq=53044&lang=ENG). However, the data are available from the NHIS (https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do) on reasonable request for researchers who meet the criteria for access to confidential data.

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REFERENCES

1. Sun H, Saeedi P, Karanunga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2021;183:109119.
2. Watada H, Takami A, Spranger R, Amano A, Hashimoto Y, Niemoeller E. Efficacy and safety of 1:1 fixed-ratio combination of insulin glargine and lixisenatide versus lixisenatide in Japanese patients with type 2 diabetes inadequately controlled on oral antidiabetic drugs: the LixiLan JP-01 randomized clinical trial. Diabetes Care. 2020;43(6):1249-1257.
3. Bell DS. Combine and conquer: advantages and disadvantages of fixed-dose combination therapy. Diabetes Obes Metab. 2013;15(4):291-300.
4. Benford M, Milligan G, Pike J, Anderson P, Piercy J, Fermer S. Fixed-dose combination antidiabetic therapy: real-world factors associated with prescribing choices and relationship with patient satisfaction and compliance. Adv Ther. 2012;29(1):26-40.
5. García-Pérez LE, Álvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D. Adherence to therapies in patients with type 2 diabetes. Diabetes Ther. 2013;4(2):175-194.
6. Banerji MA, Dunn JD. Impact of glycemic control on healthcare resource utilization and costs of type 2 diabetes: current and future pharmacologic approaches to improving outcomes. Am Health Drug Benefits. 2013;6(7):382-392.
7. Rozenfeld Y, Hunt JS, Plauschinat C, Wong KS. Oral antidiabetic medication adherence and glycemic control in managed care. Am J Manag Care. 2008;14(2):71-75.
8. Breitscheidel L, Stamenitis S, Dippel FW, Schönffski O. Economic impact of compliance to treatment with antidiabetes medication in type 2 diabetes mellitus: a review paper. J Med Econ. 2010;13(1):8-15.
9. Teresa B, Gibson P, Xue Song P, et al. Cost sharing, adherence, and health outcomes in patients with diabetes. Am J Manag Care. 2010;16(8):589-600.
10. Visaria J, Iyer NN, Raval AD, et al. Healthcare costs of diabetes and microvascular and macrovascular disease in individuals with incident type 2 diabetes mellitus: a 10-year longitudinal study. ClinicoEconomics Outcomes Res. 2020;12:423-434.
11. Böhm AK, Schneider U, Aberle J, Stargardt T. Regimen simplification and medication adherence: Fixed-dose versus loose-dose combination therapy for type 2 diabetes. PLoS One. 2021;16(5):e0250993.
12. Nishimura R, Kato H, Kisanuki K, et al. Comparison of persistence and adherence between fixed-dose combinations and two-pill combinations in Japanese patients with type 2 diabetes. Curr Med Res Opin. 2019;35(5):869-878.
13. Ko S-H, Hur K-Y, Rhee SY, et al. Antihyperglycemic agent therapy for adult patients with type 2 diabetes mellitus 2017: a position statement of the Korean Diabetes Association. Diabetes Metab J. 2017;41(5):337-348.
14. Regulation for Criteria for Providing Reimbursed Services in the NHI. http://www.hira.or.kr/bbsDummy.do?pgmid=HIRAAD200002000100&brdScnBltNo=8808&none. Accessed November 23, 2021.
15. KDA. Diabetes Fact Sheets in Korea, 2018: An Appraisal of Current Status. https://www.diabetes.or.kr/ko/pr/news/admin.php?categoryId=A&code=admin&mode=view&number=1615.
16. Kim B-Y, Won JC, Lee JH, et al. Diabetes fact sheets in Korea, 2018: an appraisal of current status. Diabetes Metab J. 2019;43(4):487-494.
17. Park J, Kwon S, Choi E-K, et al. Validation of diagnostic codes of major clinical outcomes in a National Health Insurance database. Int J Arrhythm. 2019;20(1):1-7.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic combinations in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-382.
19. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res. 2011;46(3):399-424.
20. Egede LE, Gebregziabher M, Echols C, Lynch CP. Longitudinal effects of medication nonadherence on glycemic control. Ann Pharmacother. 2014;48(5):562-570.
21. Bangalore S, Kamalakannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120(8):713-719.
22. Barner JC. Adherence to oral antidiabetic agents with pioglitazone and metformin: comparison of fixed-dose combination therapy with monotherapy and loose-dose combination therapy. *Clin Ther.* 2011; 33(9):1281-1288.

23. Schernthaner G. Fixed-dose combination therapies in the management of hyperglycaemia in type 2 diabetes: an opportunity to improve adherence and patient care. *Diabet Med.* 2010;27(7): 739-743.

24. Melikian C, White TJ, Vanderplas A, Dezii CM, Chang E. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy, *Clin Ther.* 2002;24(3):460-467.

25. Han S, Iglay K, Davies MJ, Zhang Q, Radican L. Glycemic effectiveness and medication adherence with fixed-dose combination or coadministered dual therapy of antihyperglycemic regimens: a meta-analysis. *Curr Med Res Opin.* 2012;28(6):969-977.

26. Shivaswamy V, Kedia R, Kulkarni S, Ross M. Spotlight on empagliflozin/metformin fixed-dose combination for the treatment of type 2 diabetes: a systematic review. *Patient Prefer Adherence.* 2016;10:1999-2006.

27. Blonde L, San Juan ZT. Fixed-dose combinations for treatment of type 2 diabetes mellitus. *Adv Ther.* 2012;29(1):1-13.

28. Blonde L, Wogen J, Kreilick C, Seymour AA. Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide co-administered with metformin. *Diabetes Obes Metab.* 2003;5(6):424-431.

29. Currie CJ, Peyrot M, Morgan CL, et al. The impact of treatment noncompliance on mortality in people with type 2 diabetes. *Diabetes Care.* 2012;35(6):1279-1284.

30. Raval AD, Thakker D, Vyas A, Salkini M, Madhavan S, Sambamoorthi U. Impact of metformin on clinical outcomes among men with prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis.* 2015;18(2):110-121.

31. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. *Diabetes Care.* 2012;35(12):2665-2673.

32. Suissa S. Lower risk of death with SGLT2 inhibitors in observational studies: real or bias? *Diabetes Care.* 2018;41(1):6-10.

33. Lokhandwala T, Smith N, Sternhufvud C, Sörstadius E, Lee WC, Mukherjee J. A retrospective study of persistence, adherence, and health economic outcomes of fixed-dose combination vs loose-dose combination of oral anti-diabetes drugs. *J Med Econ.* 2016;19(3): 203-212.

34. Williams SA, Buysman EK, Hulbert EM, Bergeson JG, Zhang B, Graham J. Hemoglobin A1C outcomes and health care resource use in type 2 diabetes mellitus patients treated with combination oral antidiabetic drugs through step therapy and loose-dose and fixed-dose combinations. *Manag Care.* 2012;21(7):40-48.

35. Rombopoulos G, Hatzikou M, Athanasiadis A, Elisaf M. Treatment compliance with fixed-dose combination of Vildagliptin/Metformin in patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy: a 24-week observational study. *Int J Endocrinol.* 2015;2015:251485.

36. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia.* 2009; 52(11):2288-2298.

37. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet.* 2009;373(9677):1765-1772.

38. Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int.* 2015;2015:217047.

39. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med.* 2017;167(4):268-274.

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.