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Decreased cardiovascular death in schizophrenia patients treated with antipsychotics: A Korean national cohort study

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ABSTRACT

Background: Patients with schizophrenia have a reduced life expectancy, but the association between antipsychotic usage and cause of death is uncertain.
Methods: The authors observed associations of antipsychotic usage with the mortality rate and cause of death in a population-based cohort of the Korean National Health Insurance Service database from 2003 to 2017. A total of 86,923 patients with schizophrenia were categorized by the total duration of antipsychotic prescription after schizophrenia diagnosis into treated ($n = 77{,}139$) and untreated ($n = 9784$) groups. The main outcome was all-cause mortality; causes of death included cardiovascular disease, pulmonary disease, diabetes, cancer, accident, suicide and homicide.
Results: The numbers of all-cause deaths and deaths from individual causes were significantly lower in the antipsychotic-treated group than in the untreated group (all cases, $p < 10^{-4}$). When adjusted for covariates (age, sex, income, body mass index, alcohol consumption, hypertension, cancer and cerebral stroke), mortality rates due to ischemic heart disease (hazard ratio, HR, 0.38 [95% CI, 0.18–0.77]) and stroke (HR, 0.39 [95% CI, 0.19–0.80]) were significantly lower in the antipsychotic-treated group. Among 4 atypical antipsychotics (olanzapine, risperidone, aripiprazole and quetiapine), only aripiprazole was associated with a decreased mortality risk relative to olanzapine (HR, 0.55 [95% CI, 0.32–0.96]).
Conclusions: Schizophrenia patients constantly prescribed antipsychotics had significantly lower rates of death from certain cardiovascular illnesses than untreated patients. Aripiprazole-treated schizophrenia was associated with a decreased risk of death compared with olanzapine-treated disease.

1. Introduction

Schizophrenia is a severe mental disease characterized by hallucination and delusion, which subsequently leads to the deterioration of cognitive and social functions (McCutcheon et al., 2019). One percent of the general population is diagnosed with schizophrenia in their lifetime, and its incidence is consistent across countries (Saha et al., 2005; Warner, 1995). The use of antipsychotic medication is the standard of care in the field (Harrow and Jobe, 2013), and antipsychotic use significantly facilitates recovery over the long-term course of the illness (Tandon et al., 2008). Although it has been reported that about 30% of schizophrenia obtained remission even when treated with antipsychotics at tje 10-year follow-up (Wils et al., 2017), schizophrenia has a relatively high relapse rate (1 to 10% per month) after the discontinuation of antipsychotics (Harrow and Jobe, 2013; Janicak et al., 2010). Thus, most clinicians continue to prescribe medication after acute symptoms have improved (Harrow and Jobe, 2013).

Although neurotransmitter disturbances cause schizophrenia and the pathophysiology of schizophrenia does not result in the dysfunction of major organs required for survival (Coyle et al., 2003), patients with schizophrenia have a reduced life expectancy that is more than 15 years shorter than that of the general population (Hjorthøj et al., 2017). This is partly due to the increased risk of suicide, which is approximately 22 times higher than that in the general population (Nordentoft et al., 2013). Another reason is the increased risk of coronary heart disease, which is 50 to 75% in schizophrenia, compared with 33% in the general population (Hennekens et al., 2005) and schizophrenia showed increased risk of circulatory, endocrine, pulmonary diseases after the diagnosis of a mental disorder (Momen et al., 2020). Unhealthy lifestyle habits, including smoking, alcohol consumption and a lack of exercise, are crucial factors that explain the early mortality in patients with schizophrenia (Lahti et al., 2012; Laursen et al., 2014). Antipsychotics, which are essential for the treatment of schizophrenia, have been suggested to be a possible cause of early death in this population. In particular, atypical antipsychotics are associated with weight

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gain, dyslipidemia and coronary heart disease and increase the risk of sudden cardiac death (Newcomer, 2007). Among atypical antipsychotics, olanzapine and quetiapine significantly increase the 10-year risk of coronary heart disease (Daumit et al., 2008). These reports suggested that the use of antipsychotics may be related to premature death in patients diagnosed with schizophrenia.

However, the large-scale FN11 study (11-year follow-up of mortality in patients with schizophrenia in Finland) and meta-analyses of the FDA Summary Basis of Approval data failed to find a correlation between antipsychotic use and early mortality in schizophrenia (Khan et al., 2013; Tiihonen et al., 2009), as well as another recent meta-analysis (Schneider-Thoma et al., 2018). Moreover, recent nationwide studies have reported significantly lower all-cause mortality in patients treated with antipsychotics than in those not treated (Taipale et al., 2018, 2020; Torniainen et al., 2015). Moreover, meta-analysis of 20 studies that investigated association between antipsychotic usage and mortality showed that the pooled risk for death among those using any antipsychotic was 43% lower than among those not using antipsychotics (Vermeulen et al., 2017). These studies suggest that antipsychotic treatment might lower overall mortality risk in schizophrenia, but the factors associated with low mortality rates remain unclear.

In this study, which used data from a population-based 15-year follow-up Korean database, we investigated whether prolonged treatment with antipsychotics affects the mortality rate and causes of death in patients with schizophrenia. We also investigated the association between the use of atypical antipsychotics and the all-cause mortality rate stratified by the type of medication and total prescription duration.

2. Methods

2.1. Study population

This study was conducted with a Korean population who accessed medical services in South Korea from 2002 to 2017. Among individuals who were diagnosed with schizophrenia, 20% of the entire sample was randomly extracted. The initial dataset consisted of 124,650 patients diagnosed with schizophrenia, but we excluded patients who were diagnosed with schizophrenia in 2002 ($n = 11{,}083$), as it was unclear whether that was the year they were actually diagnosed, given that it was the first year included in the dataset. Patients who had schizophrenia-related ICD codes but had never visited the psychiatric department ($n = 25{,}750$), pediatric patients (under age 10; $n = 889$) and patients with errors regarding the date of death ($n = 5$) were also excluded (Supplementary Fig. 1). Thus, a total of 86,923 patients from 2003 to 2017 were included in the analysis.

All information related to the medical services they have used was recorded in the National Health Insurance Service (NHIS) database. Anonymized data are provided after applying to and being approved by the National Health Insurance Sharing Service (NHISS), and the raw data set has approximately 100 variables, including the details of illnesses, the prescribed medications and the results of basic health examinations. The data of health examinations were administered every two years in sampled patients. In the case of multiple test results, we selected the most recent data set. The entire NHIS database includes over 50 million individuals (Seong et al., 2017), and its epidemiological profile and validity are consistently reported (Lee et al., 2017; Seong et al., 2017). The study was approved by the Institutional Review Board of the Ethics Committee of Seoul St. Mary's Hospital at The Catholic University of Korea (KC19ZESI0425).

2.2. Variables

The NHIS database contains diagnoses defined by ICD-10 (International Classification of Disease Tenth revision) codes. Individuals who had schizophrenia (ICD-10 code F20 and its subcategories) as the main diagnosis or a subdiagnosis were included in the analysis. To classify antipsychotic-treated and untreated patients with schizophrenia, we extracted a list of all prescribed antipsychotics in South Korea from 2003 to 2017 (Supplementary Table 1). If a patient diagnosed with schizophrenia had been prescribed antipsychotics for 4 weeks or during this period, they were classified in the antipsychotic-treated group. If the total duration of antipsychotic prescription was less than 4 weeks, the patients were defined as the untreated group. Individual health examination data were based on the results of the last two years as of 2013, and other variables were based on the follow-up period.

The primary outcome of this study was death. Patients with schizophrenia who died during the follow-up period had their date of death associated with their personal identification number in the NHIS database. This information was integrated with the MicroData Integrated Service (MDIS) of the Korean Statistical Information Service, and specific causes of death were recorded. The causes of death were classified according to the Korean Standard Classification of Diseases and Deaths (KCD), which follows the WHO recommendations for the medical certification of cause of death. The KCD has five stages of classification: the first stage includes 22 categories, and the second stage has 267 categories. Of these, the following categories of causes of death were used in this study: suicide (ICD codes, X60–X84); cardiovascular disease (I00-I99); COPD and pneumonia (J40-J44, J09-J18); diabetes (E10-E14); accident (V01-X59, Y85-Y89); and homicide (X85-Y09). Cardiovascular diseases were divided into 4 categories; ischemic heart disease (I20-I25); nonischemic heart disease (I00-I09, I11, I13, I26-I51); stroke (I60-I66) and other circulatory diseases (Olfson et al., 2015).

2.3. Statistical analysis

Participants who visited the hospital at least once after the diagnosis of schizophrenia were followed-up until the date of death or December 31, 2017. Starting from the index date of January 1, 2003, all antipsychotic prescription records were evaluated. In this period, a total of 21 types of antipsychotics were available in South Korea, and the prescribed dosage of each antipsychotic and the total duration of prescription in days were measured (Supplementary Table 1). To assess the health status of the participants, general health examination data from the NHIS were used. First-stage examination data, including medical interviews, postural examinations, blood tests and urine tests, were used.

Kaplan-Meier survival curves with log-rank tests were used to compare the mortality rates in antipsychotic-treated and untreated patients with schizophrenia. All causes of death were initially analyzed together, and then each of the 6 subcategories of causes of death were analyzed separately. Cox regression analysis was performed with the following covariates: the continuous variable was age (years), and the categorical variables were smoking (never, past, current), alcohol consumption (times/week, 4 categories), body mass index (4 categories), physical activity (times/week, 4 categories), hypertension (yes or no), diabetes (yes or no) and total cholesterol (mg/dl, 3 categories).

The cumulative probability of all-cause mortality was analyzed in patients taking the antipsychotics that were most commonly prescribed during the period from 2003 to 2017: olanzapine, risperidone, aripiprazole and quetiapine. In this analysis, we only included patients who were prescribed each antipsychotic as monotherapy; olanzapine-prescribed patients had no history of prescription of other types of antipsychotics. Thus, only a small number of patients were included in this analysis (the number of patients who prescriped olanzapine only during the follow-up period = 2204; risperidone = 11,970; aripiprazole = 3698; quetiapine = 10,857). Dose-related associations between antipsychotic usage and the mortality rate were evaluated with the same covariates used in the Cox regression analysis. To evaluate the association between antipsychotic prescription duration in days and the risk of mortality, Cox regression analysis with time-dependent covariates was used, and the time bin for measuring the hazard ratio was set to 100 days. All analyses were defined as significant when the two-sided

p-value was less than 0.05. Data collection, trimming and statistical analyses were performed with SAS version 9.4 (SAS Institute Inc. USA).

3. Results

3.1. Patient characteristics

The descriptive characteristics of the antipsychotic-treated and untreated patients with schizophrenia are shown in Table 1. During the 15-year follow-up period, 86,923 patients were newly diagnosed with schizophrenia. Among those, 77,139 (88.7%) were prescribed antipsychotics for at least 4 weeks, and 9784 (11.3%) were prescribed antipsychotics for less than 4 weeks or not at all. The mean total prescription duration in days of antipsychotic medications was 1482 days in the treated group and 11 days in the untreated group.

Those in the group treated with antipsychotic medications were older than the untreated group and had lower rates of cancer, hypertension and alcohol consumption. The percentage of hypertension was significantly higher in the untreated group (29.5% vs. 34.9%; treated vs. untreated groups; $p < 0.001$), but the percentage of patients who had diabetes was higher in the treated group (4.2% vs. 3.9%; treated vs. untreated groups; $p < 0.01$). The median follow-up duration of all patients was 5.86 years. The number of deaths was 10,327 (13.4%) in the treated group and 1587 (16.2%) in the untreated group. The median follow-up duration until death was 3.2 years, and the median age at the time of death was 71 years (IQR 55–82). The age at death of all participants are presented in the Supplementary Fig. 3.

3.2. Survival and causes of death

Fig. 1 depicts the Kaplan-Meier estimates for all-cause death and each category of cause of death. Patients who were not treated with antipsychotics were more likely to die than those who were treated with antipsychotics; this remained true when all causes of death were analyzed together and when each cause of death was analyzed separately (log-rank test, $p < 0.001$ in all categories). Cardiovascular diseases were the most common cause of death (treated group: 2.3%, untreated group: 3.1%), followed by cancer (treated group: 1.9%, untreated group: 2.4%). Suicide was the third most common cause of death in both the treated (1.6%) and untreated groups (1.9%) (Table 2).

As the consistent usage of antipsychotic medications had a significant effect on the mortality rate, we examined whether the lower risk for death in the treated group would be maintained when possible confounders (age, sex, income status, cancer, hypertension, diabetes, cerebral stroke, alcohol consumption and body mass index) were included. After adjusting for these covariates, the association between all-cause mortality and antipsychotic usage remained significant; the mortality rate of the antipsychotic-treated group was lower than that of the untreated group (adjusted HR, 0.79 [95% CI 0.67–0.95]).

Mortality rates due to cardiovascular diseases were different between groups; antipsychotic-treated patients with schizophrenia had a lower mortality rate than untreated patients (cardiovascular diseases: adjusted HR = 0.55 [95% CI 0.38–0.81].

Among cardiovascular diseases, deaths from ischemic heart disease were significantly lower in the treated group than in the untreated group (adjusted HR = 0.38 [95% CI 0.18–0.77]), and deaths from cerebrovascular stroke were also significantly lowered in the treated group (adjusted HR = 0.39 [95% CI 0.19–0.80]). Deaths from nonischemic heart disease were not significantly different between the two groups (adjusted HR = 0.87 [95% CI 0.40–1.94]).

When analyzed by sex, the association between the decreased mortality rate due to cardiovascular diseases and antipsychotics usage was preserved in both men and women (men: adjusted HR = 0.58 [95% CI 0.34–0.97], women: adjusted HR = 0.56 [95% CI 0.31–0.99]). Death rates from ischemic heart disease were significantly lower in treated women but not in treated men (men; adjusted HR = 0.47 [95% CI

Table 1
Descriptive characteristics of schizophrenia population.

	No. (%) of Patients			
	Total (n = 86,923)	Treated Schizophrenia (n = 77,139)	Untreated Schizophrenia (n = 9784)	p-value[a]
Age, median (IQR), year	45 (32–60)	44 (31–59)	34 (22–50)	<0.001
Sex				0.36
Men	42,353 (48.7)	37,628 (48.8)	4725 (48.3)	
Women	44,570 (51.3)	39,511 (51.2)	5059 (51.7)	
Death	11,914 (13.7)	10,327 (13.4)	1587 (16.2)	<0.001
Enrollement of Rare and Incurable Diseases[b]	33,616 (38.7)	32,465 (42.1)	1151 (11.8)	<0.001
Payment of health insurance claims, mean (SD), $	66,584 (91,874)	65,008 (91,301)	79,003 (95,365)	<0.001
Payment of health insurance claims group, 20th quartile				<0.001
Q1 (0–5)	36,993 (42.6)	33,345 (43.2)	3648 (37.3)	
Q2 (6–10)	13,420 (15.4)	11,721 (15.2)	1699 (17.4)	
Q3 (11–15)	15,024 (17.3)	13,193 (17.1)	1831 (18.7)	
Q4 (16–20)	21,486 (24.7)	18,880 (24.5)	2606 (26.6)	
Total antipsychotics prescription days, mean (SD)	1316 (1369)	1482 (1367)	11 (9)	<0.001
Diagnosis of cancer	18,058 (20.8)	15,833 (20.5)	2225 (22.7)	<0.001
Health screening in primary care	28,201 (32.4)	24,883 (32.3)	3318 (33.9)	<0.001
Hypertension (n = 20,336)	6135 (30.2)	5252 (29.5)	883 (34.9)	<0.001
Diabetes (n = 19,309)	3586 (18.6)	3203 (18.9)	383 (16.4)	<0.01
Cerebral Stroke (n = 18,188)	695 (3.8)	598 (3.7)	97 (4.3)	0.18
Smoking (n = 28,177)				<0.001
Never	18,671 (66.3)	16,528 (66.5)	2143 (64.7)	
Past	3257 (11.5)	2792 (11.2)	465 (14.0)	
Current	6249 (22.2)	5547 (22.3)	702 (21.3)	
Alcohol consumption, times/week (n = 28,162)				<0.001
0	22,170 (78.7)	19,869 (80.0)	2301 (69.5)	
1–2	4063 (14.4)	3395 (13.7)	668 (20.2)	
3–4	1202 (4.3)	986 (4.0)	216 (6.5)	
≥4	727 (2.6)	601 (2.3)	126 (3.8)	
Body mass index[c], mean (SD) (n = 28,115)	24.4 (4.1)	24.5 (4.2)	23.8 (3.8)	<0.001
<18.5	1604 (5.7)	1436 (5.8)	168 (5.1)	
18.5–22.9	9164 (32.6)	7887 (31.8)	1277 (38.6)	
23.0–24.9	5674 (20.2)	4947 (19.9)	727 (22.0)	
≥25.0	11,673 (41.5)	10,536 (42.5)	1137 (34.3)	
Total cholesterol (mg/dl), mean (SD) (n = 28,194)	190.1 (43.7)	189.8 (43.8)	191.9 (43.0)	0.05
<200	17,531 (62.2)	15,530 (62.4)	2001 (60.3)	
200–279	9907 (35.1)	8677 (34.9)	1230 (37.1)	
≥280	756 (2.7)	669 (2.7)	87 (2.6)	
HDL cholesterol (mg/dl), mean (SD) (n = 28,043)	52.6 (15.7)	52.3(15.6)	55.3 (16.2)	<0.001
<35	2285 (8.1)	2098 (8.5)	187 (5.7)	
35–59	17,854 (63.7)	15,874 (64.1)	1980 (60.3)	
≥60	7904 (28.2)	6786 (27.4)	1118 (34.0)	
Missing				
GFR[d] (ml/min), mean (SD) (n = 27,626)	88.2 (30.5)	88.1 (30.0)	89.1 (34.0)	0.06
<15	65 (0.2)	52 (0.2)	13 (0.4)	
15–59	2234 (8.1)	1989 (8.1)	245 (7.6)	
60–89	13,439 (48.6)	11,898 (48.8)	1541 (47.7)	
≥90	11,888 (43.1)	10,458 (42.9)	1430 (44.3)	

[a] Antipsychotics treated group vs. untreated group.
[b] Health insurance support for rare and incurable diseases (including schizophrenia) by Korean goverenment. Code name: V161.
[c] Calculated with the formula of weight (kg)/height^2 (m).
[d] Glomerular Filtration Rate.

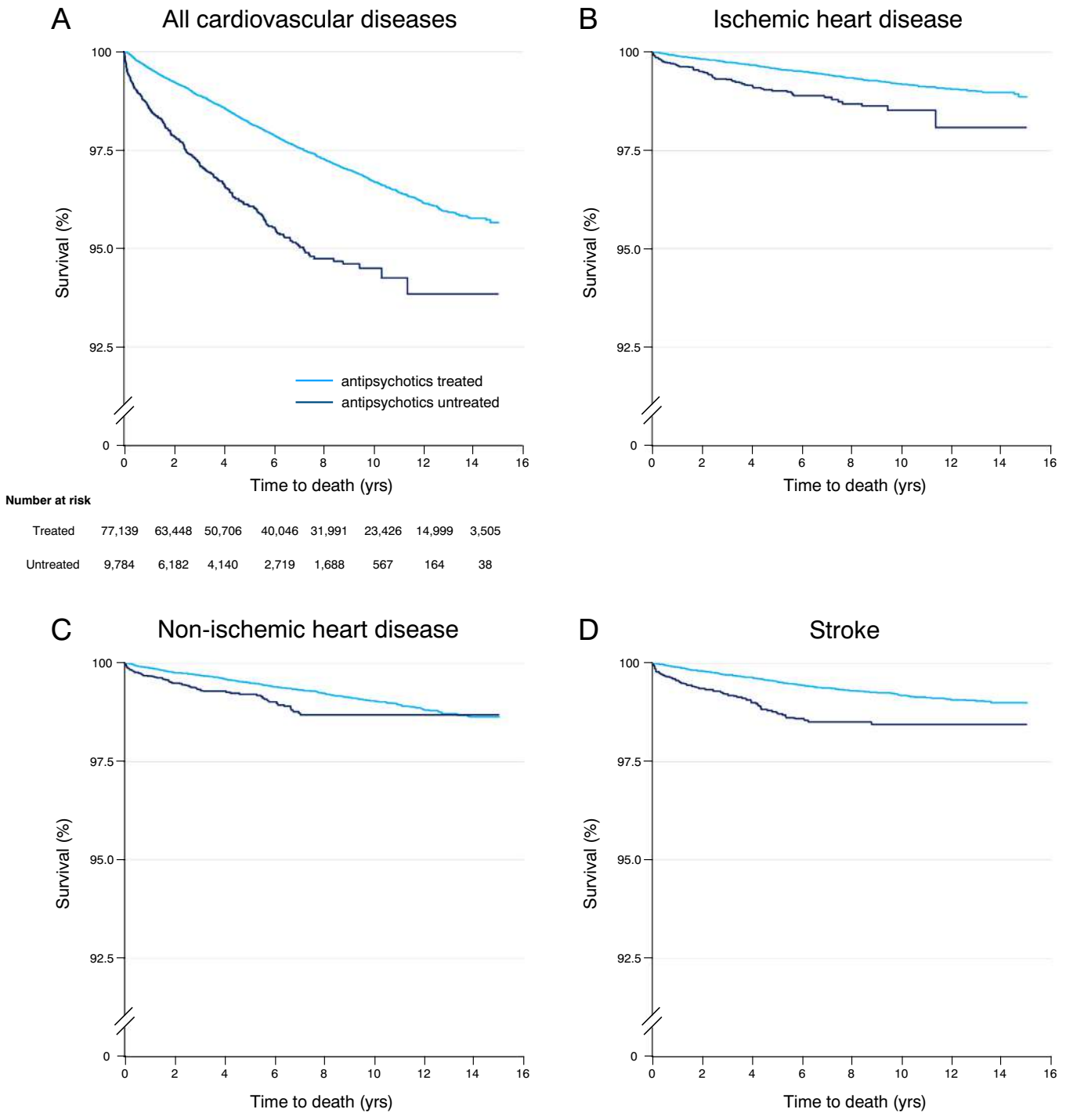

Fig. 1. Survival curve for treated and untreated patients with schizophrenia. A. Death from cardiovascular diseases (including ischemic, nonischemic heart disease, stroke and other circulatory diseases). B. Death from ischemic heart disease. C. Death from nonischemic heart disease. D. Death from stroke. A log-rank test was performed to compare groups within the same cause of death, and all groups were significantly different ($p < 0.001$).

0.19–1.17], women: adjusted HR = 0.24 [0.08–0.78]). Associations with death from other cardiovascular diseases were not statistically significant.

3.3. All-cause mortality according to the types of atypical antipsychotics

To examine whether the types of antipsychotics were associated with the relatively lower mortality rate in the antipsychotic-treated group, we evaluated the risk of death from all causes in patients treated with 4 atypical antipsychotics: olanzapine, risperidone, aripiprazole and quetiapine. In this analysis, patients who used antipsychotics in combination with other antipsychotics were not included. The total number and person-years in each group are presented in Table 3. During the follow-up period, the risperidone group had the greatest number of patients ($n = 11{,}970$, person-years = 94,224), but the death rate was the highest in the quetiapine group ($n = 10{,}857$, person-years = 48,929, incidence rate per 1000 = 48.9), followed by the olanzapine group ($n = 2204$, person-years = 12,809, incidence rate per 1000 = 22.0).

When adjusted for age, sex, body mass index, income group, diabetes, hypertension, cerebral stroke and cancer, the aripiprazole group had

Table 2
Death Toll, causes of deaths and association between antipsychotics treatment and risk of death.

	No. (%) of Patients.			Unadjusted		Adjusted[a]	
	Total (n = 86,923)	Treated Schizophrenia (n = 77,139)	Untreated Schizophrenia (n = 9784)	HR[c] (95% CI)	p-Value	HR[c] (95% CI)	p-Value
Death Toll, No. (%)	11,914 (13.7)	10,327 (13.4)	1587 (16.2)	0.52 (0.49–0.55)	<0.0001	0.79 (0.67–0.95)	0.010
Causes of death, no. (%)							
Cardiovascular Disease	2072 (2.4)	1772 (2.3)	300 (3.1)	0.47 (0.42–0.53)	<0.0001	0.55 (0.38–0.81)	0.003
Ischemic heart disease	503 (0.6)	428 (0.6)	75 (0.8)	0.45 (0.35–0.58)	<0.0001	0.38 (0.18–0.77)	0.008
Non-ischemic heart disease	594 (0.7)	525 (0.7)	69 (0.7)	0.59 (0.46–0.76)	<0.0001	0.87 (0.40–1.94)	0.739
Stroke	526 (0.6)	438 (0.6)	88 (0.9)	0.41 (0.33–0.52)	<0.0001	0.39 (0.19–0.80)	0.010
Other circulartory disease	449 (0.5)	381 (0.5)	68 (0.7)	0.45 (0.35–0.58)	<0.0001	0.73 (0.28–1.90)	0.518
COPD and Pneumonia	1098 (1.3)	979 (1.3)	119 (1.2)	0.65 (0.54–0.79)	<0.0001	0.86 (0.48–1.54)	0.609
Suicide	1450 (1.7)	1268 (1.6)	182 (1.9)	0.57 (0.49–0.67)	<0.0001	1.07 (0.66–1.76)	0.776
Cancer	1673 (1.9)	1443 (1.9)	230 (2.4)	0.50 (0.44–0.58)	<0.0001	0.77 (0.50–1.18)	0.222
Diabetes	469 (0.5)	398 (0.5)	71 (0.7)	0.45 (0.35–0.58)	<0.0001	0.73 (0.28–1.89)	0.522
Accident	503 (0.6)	426 (0.6)	77 (0.8)	0.41 (0.32–0.52)	<0.0001	0.66 (0.32–1.35)	0.250
Assault (homicide)	30 (0)	23 (0)	7 (0.1)	0.24 (0.10–0.57)	<0.01	0.26 (0.03–2.59)	0.248
Other casues of death	4619 (5.3)	4018 (5.2)	601 (6.1)	0.53 (0.49–0.58)	<0.0001	0.83 (0.60–1.16)	0.275
Men (No. of patients)	42,353	37,628	4725				
Age at the death, mean (SD)	50.1 (18.2)	50.0 (18.1)	51.0 (19.3)				
Death Toll, No. (%)	6451 (15.2)	5575 (14.8)	876 (18.5)	0.50 (0.46–0.53)	<0.0001	0.82 (0.65–1.03)	0.093
Causes of death, no. (%)							
Cardiovascular Disease	1057 (2.5)	909 (2.42)	148 (3.13)	0.48 (0.40–0.57)	<0.0001	0.58 (0.34–0.97)	0.037
Ischemic heart disease	274 (0.65)	240 (0.64)	34 (0.72)	0.54 (0.37–0.77)	<0.001	0.47 (0.19–1.17)	0.103
Non-ischemic heart disease	268 (0.63)	234 (0.62)	34 (0.72)	0.51 (0.35–0.73)	<0.001	0.55 (0.20–1.47)	0.231
Stroke	264 (0.62)	220 (0.58)	44 (0.93)	0.40(0.29–0.55)	<0.0001	0.40 (0.14–1.12)	0.080
Other circulartory disease	251 (0.59)	215 (0.57)	36 (0.76)	0.48 (0.33–0.68)	<0.0001	1.28 (0.29–5.58)	0.747
COPD and Pneumonia	663 (1.57)	596 (1.58)	67 (1.42)	0.69 (0.53–0.89)	<0.01	0.92 (0.45–1.86)	0.811
Suicide	810 (1.91)	701 (1.86)	109 (2.31)	0.52 (0.42–0.63)	<0.0001	1.15 (0.57–2.31)	0.695
Cancer	1003 (2.37)	861 (2.29)	142 (3.01)	0.49 (0.41–0.59)	<0.0001	0.96 (0.55–1.70)	0.893
Diabetes	234 (0.55)	196 (0.52)	38 (0.8)	0.42 (0.29–0.59)	<0.0001	1.12 (0.26–4.93)	0.876
Accident	311 (0.73)	263 (0.7)	48 (1.02)	0.40 (0.29–0.55)	<0.0001	0.84 (0.33–2.18)	0.725
VAssault (homicide)	19 (0.04)	13 (0.03)	6 (0.13)	0.17 (0.06–0.44)	<0.001	0.05 (0.00–1.18)	0.064
Other casues of death	2354 (5.6)	2036 (5.4)	318 (6.7)	0.49 (0.44–0.56)	<0.0001	0.74 (0.49–1.13)	0.169
Women (No. of patients)	44,570	39,511	5059				
Age at the death, mean(SD)	54.9 (19.0)	54.8 (18.9)	55.5 (20.0)				
Death Toll, No. (%)	5463 (12.3)	4752 (12)	711 (14.1)	0.54 (0.50–0.59)	<0.0001	0.76 (0.58–0.99)	0.044
Causes of death, no. (%)							
Cardiovascular Disease	1015 (2.28)	863 (2.18)	152 (3)	0.47 (0.39–0.55)	<0.0001	0.56 (0.31–0.99)	0.045
Ischemic heart disease	229 (0.51)	188 (0.48)	41 (0.81)	0.38 (0.27–0.53)	<0.0001	0.24 (0.08–0.78)	0.017
Non-ischemic heart disease	326 (0.73)	291 (0.74)	35 (0.69)	0.67 (0.47–0.95)	0.02	1.77 (0.42–7.41)	0.434
Stroke	262 (0.59)	218 (0.55)	44 (0.87)	0.42 (0.31–0.58)	<0.0001	0.39 (0.14–1.07)	0.066
Other circulartory disease	198 (0.44)	166 (0.42)	32 (0.63)	0.42 (0.29–0.61)	<0.0001	0.41 (0.11–1.48)	0.171
COPD and Pneumonia	435 (0.98)	383 (0.97)	52 (1.03)	0.59 (0.44–0.79)	<0.001	0.69 (0.24–2.01)	0.500
Suicide	640 (1.44)	567 (1.44)	73 (1.44)	0.65 (0.51–0.83)	<0.001	1.01 (0.51–2.03)	0.973
Cancer	670 (1.5)	582 (1.47)	88 (1.74)	0.53 (0.42–0.66)	<0.0001	0.58 (0.30–1.12)	0.107
Diabetes	235 (0.53)	202 (0.51)	33 (0.65)	0.49 (0.34–0.72)	<0.001	0.45 (0.13–1.56)	0.207
Accident	192 (0.43)	163 (0.41)	29 (0.57)	0.42 (0.28–0.63)	<0.0001	0.41 (0.13–1.23)	0.112
Assault (homicide)[b]	11 (0.02)	10 (0.03)	1 (0.02)	0.68 (0.09–5.47)	0.72	–	–
Other casues of death	2265 (5.1)	1982 (5)	283 (5.6)	0.57 (0.50–0.65)	<0.0001	0.89 (0.53–1.50)	0.652

[a] Adjusted for age, sex, income group, bmi group, alcohol consumption, diabetes, hypertension, cancer and cerebral stroke.
[b] Adjusted hazard ratio was not measured as there was an insufficient number of sample.
[c] Comparison of hazard ratio associated with being antipsychotics treated versus untreated.

Table 3
Risk of death according to the type of antipsychotics.

	No. (%) of Patients				Unadjusted		Adjusted[a]		Adjusted[b]	
	Total (n = 28,729)	Person-years	Death from all-causes (n = 4576)	Incidence rate per 1000	HR[d] (95% CI)	p-Value	HR[d] (95% CI)	p-Value	HR[d] (95% CI)	p-Value
Olanzapine[c]	2204	12,809	277 (12.6)	22.0	1.00 (ref)		1.00 (ref)		1.00 (ref)	
Risperidone	11,970	94,224	1808 (15.1)	19.4	0.92 (0.81–1.04)	0.19	0.88 (0.61–1.27)	0.50	0.82 (0.57–1.19)	0.30
Aripiprazole	3698	13,968	122 (3.3)	9.0	0.37 (0.30–0.46)	<0.0001	0.55 (0.32–0.96)	0.03	0.56 (0.32–0.98)	0.04
Quetiapine	10,857	48,929	2369 (21.8)	48.9	2.11 (1.87–2.39)	<0.0001	1.02 (0.72–1.44)	0.91	0.95 (0.67–1.36)	0.79

[a] Adjusted for age, sex, income group and cancer.
[b] Adjusted for age, sex, body mass index, income group, diabetes, hypertension, cerebral stroke and cancer.
[c] Patients who were only prescribed olanzapine, not other antipsychptics, during the follow-up period.
[d] Comparison of hazard ratio associated with being antipsychotics treated versus untreated.

a lower risk of death from all causes than the olanzapine group (HR = 0.56 [95% CI 0.32–0.98]). An increase in the prescription duration by 100 days did not significantly affect the all-cause mortality rate in any group (Supplementary Table 3). When we classified patients into 4 groups according to prescription duration, there was also no significant difference in the mortality risk in any group (Supplementary Table 4).

The cumulative probability of all-cause mortality in each group is presented in Fig. 2A. The quetiapine group had the highest mortality rate in the entire treatment period, followed by the olanzapine and risperidone groups. Aripiprazole-treated patients had the lowest probability of all-cause mortality during the follow-up period. Fig. 2B shows the association between all-cause mortality and antipsychotic prescription duration adjusted for covariates. In all 4 atypical antipsychotic groups, the mortality risk was significantly increased within 500 days of treatment, but the risk decreased as the prescription duration increased. This nonlinear association was significant only in the quetiapine-treated group, and aripiprazole lost statistical significance, with a large variation and a large 95% CI.

4. Discussion

In this nationwide population-based study of 86,923 patients with schizophrenia, long-term treatment with antipsychotic agents lowered the risk of death from cardiovascular diseases but not from other causes of death. Among the 4 categories of atypical antipsychotics, aripiprazole was associated with decreased all-cause mortality compared with olanzapine.

Our findings of a decreased overall mortality risk in antipsychotic-treated patients with schizophrenia are in line with the previous findings of the US Food and Drug Administration (FDA) Summary Basis of Approval reports (Khan et al., 2013) and of the nationwide registers of Sweden (Torniainen et al., 2015). Khan et al. found that the overall mortality rate among antipsychotic-treated schizophrenia patients was significantly lower than that in the placebo group, with an odds ratio of less than one half (Khan et al., 2013), similar to our result (adjusted HR, 0.79 [95% CI 0.67–0.95]). In Khan et al.'s study, the proportion of patients who received antipsychotic agents for more than 360 days was 9.5%, and the total exposure duration was 9618 years; in our study, the person-years in the antipsychotic-treated group was 527,655, and that in the untreated group was 39,483. Thus, our findings suggest that the association between antipsychotic usage and reduced overall mortality risk may persist over longer treatment periods than previously suggested.

In detailed analysis of causes of death, we found that antipsychotic use lowered the risk of death from ischemic heart disease and stroke after adjusting for covariates. These results suggest that the usage of antipsychotic drugs may be effective in protecting against death from ischemic heart disease but not death from nonischemic heart disease. This is contrary to expectations, as previous studies have reported that antipsychotics have a negative effect on the development of cardiovascular diseases, especially coronary heart disease (Daumit et al., 2008; Raedler, 2010).

Regardless, the association between cardiovascular diseases and antipsychotic usage varies depending on the type of agent, and other medical conditions caused by antipsychotics (e.g., weight gain, diabetes and dyslipidemia) may affect the development of cardiovascular diseases (Raedler, 2010). Even after adjusting for such covariates (BMI, hypertension and diabetes), we found that over 15 years of follow-up, death due to ischemic heart disease and stroke was significantly reduced in antipsychotic-treated men and women with schizophrenia. These results suggest that prolonged use of antipsychotic agents might have a protective effect on cardiovascular diseases that are caused by vascular occlusion in patients with schizophrenia.

The rate of suicide, which is a common cause of death in psychiatric patients (Roy, 1982), between the antipsychotic-treated and untreated groups was not significantly different. Previous studies have reported that suicide is the main cause of death in schizophrenia patients (Carlborg et al., 2010; Hor and Taylor, 2010). In our NHIS database, deaths from suicide (1.7%) were much lower than the estimated suicide risk in patients with schizophrenia, which is approximately 4 to 5% (Carlborg et al., 2010). This might be related to the social stigma associated with suicide (Blumenthal, 1988). Indeed, there is a very negative view of suicide in South Korea (Lee and Ahn, 2015). Thus, it is possible that a large proportion of deaths with unclear causes were classified as nonsuicidal accidental deaths (Seo, 2001).

Previous studies have investigated the preventive effect of antipsychotic drugs on death from suicide. In an 11-year follow-up study of schizophrenia patients, suicide rates decreased in those treated with antipsychotics (Tiihonen et al., 2009), though in a meta-analysis study the decreased risk was not statistically significant due to low statistical power (Leucht et al., 2012). Our findings suggest that long-term use of antipsychotics might contribute to lowering all-cause mortality but

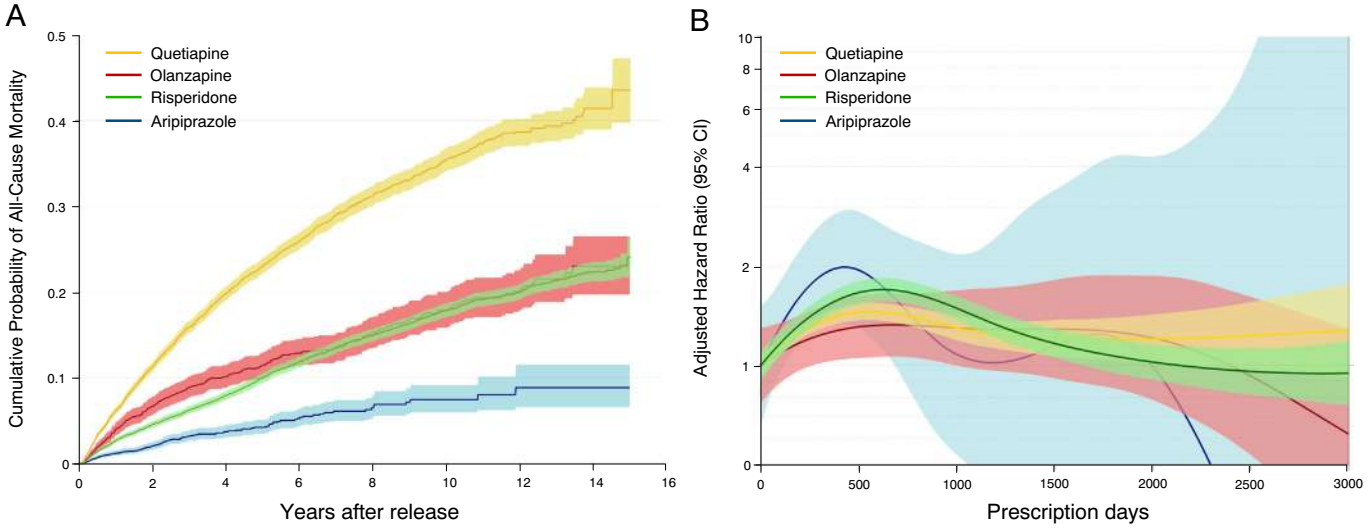

Fig. 2. Association between all-cause mortality and atypical antipsychotic group by prescription duration. A. Cumulative probability of all-cause mortality associated with 4 atypical antipsychotics. B. Hazard ratio for all-cause death in each antipsychotic group. Risk was measured relative to patients who never used antipsychotics. The shaded area represents the 95% confidence interval.

might not prevent suicide. However, it should be noted that antipsychotic used before discontinuation cannot protect against suicide.

The effect of certain atypical antipsychotics on cardiovascular diseases remains an important issue. Although antipsychotic agents may directly increase cardiac risk to some degree, indirect aspects related to poor lifestyle habits and weight gain are also relevant (Drici and Priori, 2007; Raedler, 2010). Due to a number of missing data points and missing covariates, we could not assess the association between atypical antipsychotics and each cause of death. Furthermore, among the 21 antipsychotics examined in this study, only 4 atypical ones were selected for analysis. Nonetheless, the 4 antipsychotics evaluated in the analysis are the most commonly used in clinical practice (Ilyas and Moncrieff, 2012), and we found that the aripiprazole group had an all-cause mortality rate (HR = 0.55 [95% CI 0.32–0.96]) that was approximately half that of the olanzapine group. Although only basic sociodemographic variables and a diagnosis of cancer were used as covariates, this result is consistent with previous findings. Aripiprazole has a more neutral metabolic profile than other atypical antipsychotics (Kerwin et al., 2007) and may be associated with a lower risk of cardiovascular events than olanzapine (Citrome et al., 2013). Thus, the decreased all-cause mortality rate in the long-term aripiprazole-treated group might be related to its associated low risk of cardiovascular diseases.

Despite no significant association when the prescription duration was increased by 100 days, HRs for all-cause mortality according to total prescription duration revealed nonlinear associations over time (Fig. 3). When the total prescription duration was fewer than 500 days, all 4 atypical antipsychotics were related to significantly higher risks of death, but the risks decreased after 500 days, even though there was no statistical significance except for in the quetiapine group. As this analysis only targeted all-cause mortality and disease-related covariates were not included, it is difficult to infer how short-term or mid-term use of these antipsychotic agents affects overall mortality. Nevertheless, there is a possibility that unexpected death from antipsychotics (Titier et al., 2005) or poor adherence to treatment in an earlier treatment period may be related to this finding.

Although this study used a population-based dataset with 15 years of follow-up of patients with schizophrenia, it has several limitations. First, as we only defined schizophrenia based on the ICD-10 codes, there remains the possibility that relevant diagnostic codes were used when antipsychotics were actually prescribed for the treatment of other diseases (e.g., delirium). However, we included participants who had a history of visits to the psychiatry department (both inpatient and outpatient), and thus, the diagnosis of schizophrenia was confirmed at least once by a psychiatrist. Nevertheless, further research could be performed to compare the effects of antipsychotics on death in patients with other mental illnesses. Second, there is uncertainty regarding accidental deaths, which was the most common cause of death in our study. Although Statistics Korea complements uncertain causes of accidental death using other administrative databases (e.g., National Police Agency, National Forensic Service), there is a possibility that impulsive suicides and deaths for which suicide was not the clear cause could have been classified as accidental deaths rather than as suicides. Fourth, the main analysis of this study was based on follow-up years and not person-year exposure. This may have resulted in exclusion of patients who were not steadily taking antipsychotics from the treatment group, but our supplementary results suggest that most patients treated with antipsychotics took their medication until their death (Supplementary Fig. 2). Last, among the 21 types of antipsychotics included in this study, the effects of typical antipsychotics on mortality were not analyzed. Typical and atypical antipsychotics are associated with comparable risks of sudden cardiac death (Ray et al., 2009), but the number of participants who used typical antipsychotics alone was insufficient for the analysis. Further studies that include various types of antipsychotic agents are needed to validate the results of this study.

5. Conclusions

In patients with schizophrenia who were diagnosed and treated from 2003 to 2017 in South Korea, people who were treated with antipsychotic agents had lower risks of death from ischemic heart disease and stroke than those who were not treated. Among the atypical antipsychotics, aripiprazole was associated with a lower all-cause mortality rate than olanzapine.

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Drafting the manuscript: J. Oh and T.-S. Kim.
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Declaration of competing interest
The authors declare that there are no conflict of interests.

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