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Trimetazidine use and the risk of parkinsonism: a nationwide population-based cohort study in Korea

Trimetazidine의 사용과 파킨슨증 발생 위험: 전국 인구기반 코호트 연구

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이 논문을 약학박사 학위논문으로 제출함
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Abstract

Trimetazidine use and the risk of parkinsonism: a nationwide population-based cohort study in Korea

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The real-world data (RWD) has received considerable interest globally and the real-world evidence derived from the analyses of RWD has been compiled to complement research findings with limitations from traditional clinical trials. To date, RWD has become an important tool in postmarketing surveillance to monitor the safety of drugs. In South Korea, the health insurance claim database which contains sample data from a representative Korean population is provided by the government. Trimetazidine, an anti-anginal drug with documented tolerable safety, has been used in many countries from Europe and Asia. However, the safety concerns of trimetazidine-induced parkinsonism have been raised based on cumulated adverse event cases. Since trimetazidine was not

approved by the U.S. Food and Drug Administration and regulatory agencies from other countries, access to the latest information on drug safety has been less optimal. Also, the evidence of trimetazidine-associated parkinsonism has mostly relied on case reports and small observational studies, and the large-scale population-based studies to quantitatively evaluate the risk were scarce. Therefore, we aimed to investigate the risk of trimetazidine-induced parkinsonism using national health claim data.

A propensity score-matched retrospective cohort study assessing the risk of trimetazidine-induced parkinsonism was conducted using data from the National Health Insurance Service—National Sample Cohort 2.0, between 2002 and 2015. A 4-year washout period was placed to identify new trimetazidine users detected between 2006 to 2007, and non-trimetazidine users were matched to trimetazidine users in a ratio of 3:1 by greedy matching. Any covariates including sociodemographic characteristics, concurrent medications, and comorbid clinical conditions were captured from 2002 to 2007, and the study outcome of a new parkinsonism event was detected during the 8-year follow-up period. The risk of parkinsonism was evaluated using multivariate Cox proportional hazard regression analysis, adjusted for sex, age, insurance type, area of residence, comorbidities, and concurrent

medications.

A total of 9,712 trimetazidine users and 29,116 matched non-trimetazidine users were included. Trimetazidine users had a significantly higher incidence rate of parkinsonism than non-trimetazidine users (9.34 vs. 6.71 per 1,000 person-years; $p < 0.0001$). Trimetazidine use significantly increased the risk of parkinsonism (adjusted hazard ratio = 1.38; 95% CI = 1.26-1.51). Cumulative incidence showed an increasing trend with higher cumulative doses of trimetazidine, compared with non-trimetazidine use ($p < 0.001$). Trimetazidine users who were concurrently on other medications had a higher risk of parkinsonism than trimetazidine users who were not on other medications (p for trend = 0.005).

This is the first population-based study identifying the risk of parkinsonism associated with trimetazidine. The findings indicated that trimetazidine use significantly increased the risk of parkinsonism. Closer monitoring should be considered for trimetazidine users, especially for those who are older, using trimetazidine at high cumulative doses and other parkinsonism-inducing medications.

Keywords : Trimetazidine, Drug-induced parkinsonism, Anti-

anginal drug, Health insurance claim data, Epidemiologic study.

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Chapter 1. Introduction

1.1. Pharmacovigilance Study Using Real-World Data

Beyond the randomized controlled clinical trials, the utilization of real-world data (RWD), especially for the safety evaluation, has received substantial attention from the researcher, as well as regulatory agencies in recent years [1, 2]. The RWD collected from electronic health records, registry, claims, and billing data was defined as data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources by the United States Food and Drug Administration (U.S. FDA) [3]. To date, RWD has been used widely including for postmarketing surveillance to monitor the safety of drugs, and various efforts to harmonize RWD to support regulatory decision making have been evolved globally [1, 4].

As compared to the randomized controlled trials (RCT), the benefits of using RWD are already acknowledged by health services researcehrs [2]. Studies using RWD have fewer restrictions on the study population as they can involve pregnant women, children, or vulnerable participants with many comorbidities which are often

excluded in the RCT [5]. Also, findings from RWD can offer greater generalizability since the RWD reflects the real-world clinical setting, patient population, and practice. Moreover, studies based on RWD are efficient in way of time and cost-saving [6]. Despite the benefits of RWD uses, the concern on RWD analyses, specifically the biases and confounding factors, remains [5]. For example, the selection bias which resulted in an imbalance of baseline characteristics due to unequal distribution of the study population is a well-known threat to the internal validity of RWD analyses [7]. In the case of a longitudinal follow-up study, immortal time which causes a bias in favor of treatment effect can be generated [8]. Additionally, classification errors (also known as misclassification bias) and insufficient completeness and accuracy of datasets are typically recognized as the limitations of RWD analyses [2, 9]. Therefore, applying well-structured study designs and rigorous evaluation via various statistical methods are required to avoid common flaws when RWD analyses are conducted [5].

While the weakness of reliability cannot be ignored, it is believed that the real-world evidence (RWE) derived from analysis of RWD can bridge the knowledge gap in the clinical area where traditional clinical trials would not be feasible [10]. In South Korea, due to the universal coverage health insurance system for all

citizens, the health insurance claim database which contains a representative Korean population sample is provided as one of the great RWD by the government [11, 12].

Since the safety issues associated with some medications became raised such as nicorandil-associated ulcerations, trimetazidine induced parkinsonism, or respiratory concerns of gabapentin in South Korea, proper regulatory actions including releasing a warning letter or changing the insert paper were taken [13, 14]. However, the detailed safety information including the risk level or incidence rate is quite difficult to ascertain because the evidence of safety problems has mostly relied on case reports. In particular, access to the latest safety information of some medications not approved by the U.S. FDA but used in South Korea has been less optimal due to low interests and a limited number of large-scale studies [14]. Therefore, generating the RWE of safety problems related to these medications focused on the Korean population is crucial to healthcare professionals including prescribers and pharmacists, as well as the regulatory agency for prompt regulatory actions.

1.2. Characteristics of Trimetazidine

Trimetazidine [1-(2,3,4 trimethoxy benzyl)-piperazine dihydrochloride] is an agent initially approved in 1978 from France for angina pectoris, dizziness, and tinnitus (Figure 1) [14, 15]. Although this agent was not approved by the U.S. FDA, it has been widely available on the European and Asian markets with reasonable efficacy and safety profile [16]. The exact mechanism of action of trimetazidine on angina pectoris and tinnitus has not been fully elucidated, but its role as metabolic regulator and its cytoprotective effects have been described from in vitro/in vivo studies [17]. Trimetazidine promotes more efficient glucose oxidation than beta-oxidation of fatty acid through direct inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, which results in reducing the oxygen consumption in cardiomyocytes [18]. Since the conventional anti-anginal agents like β-blockers, calcium channel blockers (CCBs), or nitrates have a more direct effect on hemodynamic responses which exert their anti-ischemic by changing heart rate, coronary flow, contractility, and blood pressure, trimetazidine has been mostly recommended as second-line therapy in combination with or substitute for conventional agents [19]. Trimetazidine also has been shown to have cytoprotective properties with anti-inflammatory and anti-

apoptotic effects as demonstrated by the increased miR-21 expression [17]. Cytoprotective effects of trimetazidine were known to prevent injuries to neurosensorial tissues, thereby its use in the field of otorhinolaryngology including tinnitus, vertigo, or Meniere's disease was supported [20]. Also, the role of trimetazidine in various clinical conditions, such as contrast-induced nephropathy [21], heart failure [22], and peripheral artery disease [23], has been newly proposed in some early clinical studies.

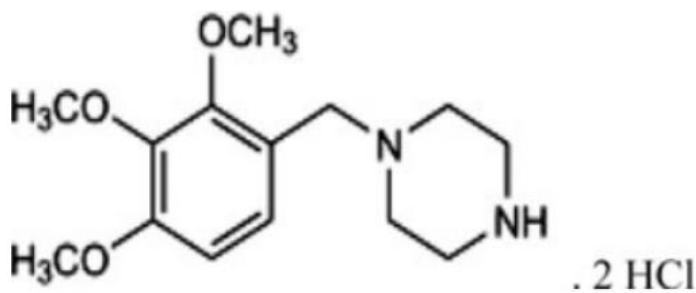

Figure 1. The chemical structure of trimetazidine.[15]

1.3. Safety issue of Trimetazidine

1.3.1. Drug-induced Parkinsonism

Parkinson's disease (PD) is the second most common neurodegenerative disorder, with a growing prevalence worldwide as the aging population increases [24]. The prevalence of PD was reported 315 per 100,000 persons and 181.3 per 100,000 persons of all ages from a meta-analysis [25] and a recent cross-sectional study in South Korea, respectively [26]. Drug-induced parkinsonism (DIP)— secondary parkinsonism—is defined as the development of parkinsonian symptoms including resting tremor, muscular rigidity, akinesia, or bradykinesia after being treated with dopamine-blocking or -depleting drug [27]. Unlike idiopathic Parkinson's disease (iPD), DIP often shows different clinical characteristics, including symmetrical features and female predominance [28, 29], but the differential diagnosis between DIP and iPD based solely on the clinical manifestation may not always be feasible [30]. Therefore, the epidemiologic data or studies on DIP were limited and may be inaccurately described since DIP is often misdiagnosed as iPD or unrecognized. According to some population-based studies, DIP was reported as accounting for approximately 12-20% of patients with parkinsonism [27, 31], and

a study by Savica et al, presented that the incidence of DIP was 3.3 per 100,000 person-years in all age groups [27].

In South Korea, two population-based studies [26, 32] showed consistent results that prevalence and incidence of DIP increased steadily although the suggested prevalence rates from each study were quite different. A retrospective study using the National Service Health Insurance Claims database [32] provided that the annual prevalence of DIP was 4.09 and 7.02 per 100,000 persons in 2009 and 2015, respectively, whereas another population-based study using the Health Insurance Review and Assessment Service database [26] reported that the prevalence of DIP in 2012 and 2015 was 7.3 and 15.4 per 100,000 persons, respectively. The incidence of DIP was reported as 7.1 and 13.9 per 100,000 person-years in 2012 and 2015, respectively [26].

Numerous medications have been known to increase the risk of developing DIP [28, 29, 33, 34]. Several studies have provided a list of parkinsonism-inducing medications classified by their relative risk of developing DIP [28, 29]. Although the suggested risk levels of medications are varied from studies, typical and atypical antipsychotics, gastrointestinal prokinetics/anti-emetics, and dopamine depleters were mostly considered as high-risk drugs. Some calcium channel blockers and anti-histamine agents that were

prescribed for nausea, vomiting, vertigo, and Meniere's disease, i.e. flunarizine and cinnarizine were provided as intermediate- to high-risk drugs, and anti-epileptics, mood stabilizers, diltiazem, and verapamil were reported as intermediate-risk drugs. Other drugs including anti-arrhythmic agents, anti-depressants, statins, and some anti-microbial agents were recognized as drugs infrequently causing parkinsonism [28, 29].

Typical and atypical antipsychotics are one of the high-risk parkinsonism-inducing medications with well-established causative mechanisms as D_2 dopamine receptor blockade in animal studies [29]. Since the typical antipsychotics are potent blockers of striatal D2 receptors whereas atypical antipsychotics have lower potency of the blockade as a transient binding of D_2 receptors, the typical antipsychotics were considered to be at a greater risk of parkinsonism [28]. However, high-dose atypical antipsychotics showed a similar risk of parkinsonism to typical antipsychotics in the real-world clinical situation since D_2 receptor binding was identified in a dose-dependent manner [35].

The gastrointestinal prokinetics including metoclopramide, levosulpiride, and clebopride were one of the other dopamine receptor blockers and have also been associated with DIP and considered high-risk medications [36, 37]. In addition to the

blockade of enteric inhibitory D_2 receptor which leads to a prokinetic effect, the antagonizing of central D_2 receptor induces the parkinsonism side effect in some prokinetic which can cross the blood–brain barrier [37].

Parkinsonism may also be caused by other medications. Dopamine depleters that inhibit the uptake of dopamine into granular vesicles induce parkinsonism by depleting dopamine in the presynaptic terminal [38]. CCBs [39] and anti–epileptic drugs [40] are also suggested as intermediate–risk medications although the exact pathogenic mechanisms are not yet fully understood. CCBs, including cinnarizine and flunarizine, may cause parkinsonism by direct blocking the D_2 receptor or reducing neurotransmission of dopamine [41]. Regarding a pathogenic mechanism of DIP by anti–epileptics, mitochondrial chain dysfunction was proposed [40]. The schematic figure on the pathogenesis of DIP was presented in Figure 2 [38].

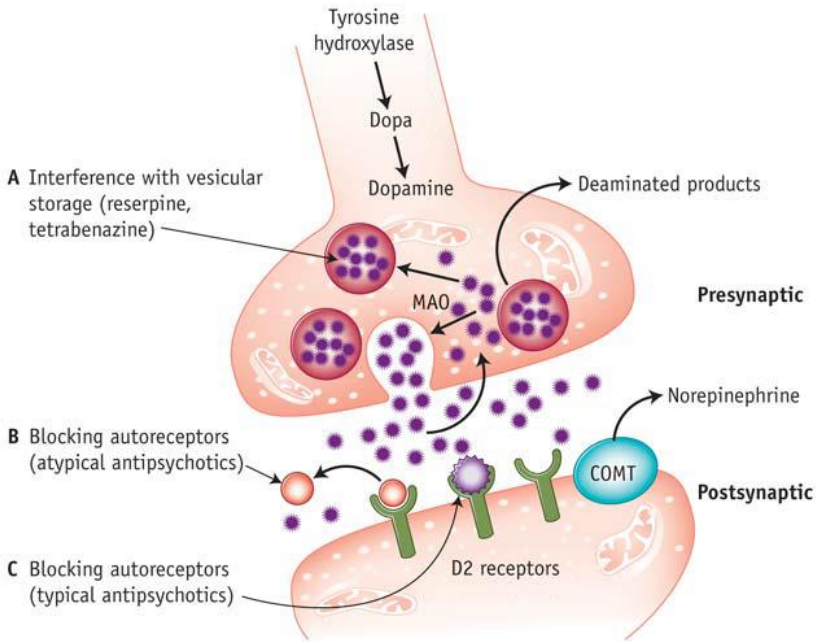

Figure 2. Schematic figure on pathogenesis of drug-induced parkinsonism. COMT, catechol-O-methyltransferase; MAO—monoamine oxidase. [38]

Although the clinical features of DIP are varied in patients, iPD cases were reported to present different features [33]. DIP was reported to be more prevalent in women and the mean age of the disease onset was greater [33]. Unlike iPD which is characterized by asymmetric body signs, the DIP often shows symmetrical movements and the presence of tremor is variable [33]. Patients with DIP show poor response to anti-parkinsonism medication such as L-DOPA and dopamine agonists. Most cases of DIP were reported as reversible by the withdrawal of offending drugs unless subclinical parkinsonism was unmasked or preclinical parkinsonism was worsened by the drugs [42]. It has been reported that parkinsonism persists or progresses in up to 25% of DIP cases despite the drug discontinuation [34].

1.3.2. The Risk of Trimetazidine-associated Parkinsonism

While trimetazidine is generally considered as a well tolerable drug with mild adverse drug reactions including gastrointestinal disturbance, nausea, vomiting, and diarrhea, the rare but reversible side effects associated with motor function have been reported in many studies [14, 43]. The reversible parkinsonism was initially reported in eight trimetazidine users by Marti Masso in 2004 [44], and since then, a larger observational study also identified trimetazidine-induced parkinsonism, gait disorders, and tremor, and evaluated the occurrence rate (43%) of movement disorder by trimetazidine [45]. Another study using spontaneous ADR reporting data over 6 years (from 2005 to 2011) in France identified 21 cases of extrapyramidal disorders associated with trimetazidine [43]. In light of accumulating reports of the adverse neurological effects of trimetazidine, the European Medicines Agency (EMA) re-evaluated the safety of trimetazidine and made a recommendation of restricting the use of trimetazidine to add-on therapy only for the symptomatic treatment of stable angina pectoris [46]. Although these adverse events are uncommon and reversible, the EMA also recommended contraindicating trimetazidine in patients with PD or parkinsonian symptoms [46].

Since the safety recommendation from EMA for the careful

use of trimetazidine has been issued less than a decade ago, only a few studies examined trimetazidine-associated parkinsonism. According to a recent prospective study by Pintér et al [42], trimetazidine-associated parkinsonism showed mild clinical features and symmetrical motor symptomatology, consistent with those of DIP. In this study, 11 cases (33%) were identified as reversible after trimetazidine discontinuation from 33 trimetazidine-induced parkinsonism cases [42]. Our previous cross-sectional study using 1-year data in Korea [47] presented that trimetazidine use was a significant contributing factor of a new diagnosis of parkinsonism (adjusted odds ratio [aOR] = 1.39) and about 2.5% of trimetazidine users already had preexisting extrapyramidal and movement disorder in Korea. The results showed that the safety recommendation from the regulatory agency was not followed strictly enough in the clinical situation.

Trimetazidine has not been well documented as a parkinsonism-inducing medication in previous DIP-related studies [27, 29, 38] and was not even mentioned as a risk drug in all recent DIP-related epidemiology studies conducted in Korea [26, 32, 48]. Moreover, while other parkinsonism-inducing medications have been investigated in several large-scale epidemiological studies [49], few studies have examined trimetazidine-associated

parkinsonism, and even fewer have used population-based data and robust study designs. So far, trimetazidine-associated parkinsonism was somewhat neglected and surely less recognized by researchers as well as clinicians due to the limited safety information. The production and optimal access of drug safety data are crucial to evidence-based pharmacotherapy by healthcare professionals. Therefore, a nationwide study using RWD based on the Korean population to provide detailed safety information of trimetazidine-associated parkinsonism reflecting the reality of clinical practice is needed.

1.4. Purpose of Research

This study aimed to investigate and describe the risk of trimetazidine-induced parkinsonism based on the Korean population. We conducted a retrospective cohort study using a 14-year longitudinal national-level healthcare claims database in South Korea to investigate the association between the use of trimetazidine and the risk of developing parkinsonism. We specifically analyzed the data to estimate the incidence rate and overall risk and to describe the cumulative dose-response relationship and the combined effects of trimetazidine with concurrent use of other parkinsonism-inducing medications.

Chapter 2. Methods

2.1. Data Source

A retrospective cohort study was conducted using data from the National Health Insurance Service—National Sample Cohort (NHIS-NSC) 2.0, between 2002 and 2015. The NHIS is a single-payer healthcare system, providing universal health insurance coverage to all South Korean citizens, and generates research-ready cohort databases from insurance claims with selected demographic (age, sex, and insurance type) and clinical information. The NHIS-NSC database comprised about 2.2% of the total eligible Korean population in 2006, who were selected by a systematic stratified random sampling method, considering age, sex, eligibility status, and income level, as a representative sample of the general South Korean population. The research database was constructed by following up the selected participants retrospectively for 4 years (2002-2005) and prospectively for 10 years (2006-2015) [11].

The individual records from the NHIS-NSC data were anonymized and de-identified by the Health Insurance Review and Assessment Service, mandated by the Personal Information Protection Act and National Health Insurance Act, prior to researchers accessing the data. All research was performed in

accordance with the ethical requirements of the Seoul National University IRB and approved by the IRB without the requirements for obtaining written informed consent (IRB No. E1808/003-011).

2.2. Study Population

Adult individuals aged over 19 years in 2002 (n=725,224) were selected from the NHIS-NSC database. The study period, which included the collection of longitudinal data from January 2002 to December 2015, was divided into two periods on either side of an index date (January 1, 2008) as (1) "exposure ascertainment period" (January 2002 to December 2007); and (2) "follow-up period" (January 2008 to December 2015). We collected data on sociodemographic characteristics, prescriptions of trimetazidine and any concurrent medications, and comorbid clinical conditions during the "exposure ascertainment period". The study outcome, a new event of parkinsonism, was captured during the "follow-up period". The participants were followed from January 1, 2008, until the date of the event of parkinsonism, death, or the administrative censoring (December 31, 2015).

To include only patients who were using their first trimetazidine in the identification period which was from January 2006 to December 2007, the participants who were prescribed trimetazidine for the first time before or after this period were excluded (n=51,823). Participants with diagnoses of extrapyramidal symptoms or movement disorders prior to the follow-up period were excluded (n=9,917) based on the following

International Classification of Diseases, Tenth Revision (ICD-10): Extrapyramidal and movement disorders (G20-G26). Also, participants who had died before the starting of the follow-up were excluded (n=4,307). The participants with a government-rated disability grade due to a brain abnormality prior to the follow-up period were excluded (n=2,653) since brain abnormality is a documented risk factor for parkinsonism [50]. Excluding the total of 68,700 participants who met the exclusion criteria, the remaining 656,524 patients were included in the study cohort after the selection procedure.

2.3. Data Collection

The primary exposure of interest was trimetazidine use. The exposure variable was defined as one or more prescriptions of trimetazidine with one day or more duration. Medication codes, dosage, frequency, and duration for trimetazidine prescription were collected in the identification period. Patients with no records of trimetazidine prescriptions were assigned as a non-trimetazidine user group.

The accumulated dose of trimetazidine was calculated by multiplying the trimetazidine dosage, frequency, and days' supply to evaluate the cumulative dose-response relationship. Since two different doses of trimetazidine as 20mg and 35mg have been marketed in South Korea, we used the defined daily dose (DDD), which was developed by the World Health Organization (WHO), to convert accumulated doses into DDD [51]. Cumulative DDDs (cDDD) are the total sum of the DDD in each individual representing total exposure for trimetazidine. Depending on the level of cumulative doses, trimetazidine users were divided into three groups: (1) ≤7 cDDDs; (2) 7-30 cDDDs; and (3) >30 cDDDs.

The study outcome was a new occurrence of parkinsonism during the follow-up period, which was identified and confirmed when a patient was recorded with the following ICD-10 diagnostic

codes at least three times, in either an inpatient or outpatient setting: G20, G21.1, G21.2, G21.8, G21.9, and G24–G26 (Table 1). The date of the outcome was defined as the first date of the appearance of the aforementioned diagnostic code.

Table 1. List of ICD-10 codes for study outcome.

Disease	ICD-10 code
Parkinson's disease	G20
Other drug-induced secondary parkinsonism	G21.1
Secondary parkinsonism due to other external agents	G21.2
Other secondary parkinsonism	G21.8
Secondary parkinsonism, unspecified	G21.9
Dystonia	G24.0-G24.9
Other extrapyramidal and movement disorders	G25.0-G25.9
Extrapyramidal and movement disorders in diseases classified elsewhere	G26

Abbreviation: ICD-20, International Classification of Diseases, Tenth Revision.

2.4. Confounders

Sociodemographic characteristics, including the patient's age, sex, area of residence, insurance type, and death record, were collected. The presence of comorbid diseases and concurrent medications relating to the trimetazidine use and known to independently increase the risk of parkinsonism from the literature review were identified during the "exposure ascertainment period" which was 6 years prior to the index date [52, 53].

Comorbid conditions included diabetes mellitus, end-stage renal disease (ESRD), stroke, dementia, hypertension, ischemic heart disease, dyslipidemia, head injury, and severe liver disease [52-54]. If the patients had one or more claims with the ICD-10 code of comorbid disease, they were assigned as having comorbidities. Regarding the concurrent medications, typical and atypical antipsychotics, prokinetics, CCBs, anti-epileptics, and dopamine depleters [28, 29] were included. The patients who had one or more prescription claims of medications with the duration of one or more days were considered as concurrent medication users. ICD-10 codes for the comorbid diseases and details of concurrent medications are shown in Tables 2 and 3.

Table 2. List of ICD-10 codes for comorbid disease.

Disease	ICD-10 codes
Diabetes mellitus	E10-E14
End stage renal disease	N18.5
Stroke	I60-I69, G45, G46
Dementia	G30
Hypertension	I10-I15
Ischemic heart disease	I20-I25
Dyslipidemia	E78
Head injury	S01.9, S06.0-S06.6, S06.8, S06.9, S09.1, S09.8, S09.9
Severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5-K76.7

Abbreviation: ICD; International Classification of Disease 10th Revision

Table 3. List of concurrent medications.

Drug Class	Drug name
Typical Antipsychotics	Chlorpromazine Chlorprothixene Flupentixol Haloperidol Levomepromazine Perphenazine Pimozide Thioridazine Thiothixene Zuclopenthixol
Atypical Antipsychotics	Amisulpride Aripiprazole Clozapine Olanzapine Paliperidone Quetiapine Risperidone Sulpiride Ziprasidone Zotepine
Prokinetics	Clebopride Levosulpiride Metoclopramide Prochlorperazine Sulpiride*
Calcium channel blockers	Cinnarizine Diltiazem Flunarizine Verapamil
Anti-epileptics	Levetiracetam Phenytoin Valproate
Dopamine depeleters	Reserpine Tetrabenazine

*Some products of sulpiride were approved as a prokinetic by Ministry of Food and Drug Safety, the Republic of Korea.

2.5. Statistical Analysis

The propensity score (PS) for trimetazidine use was estimated using a multivariate logistic regression model with consideration of predictor variables, including sex, age, insurance type, area of residence, comorbid diseases, and concurrent use of parkinsonism-inducing medications. Among the entire non-trimetazidine user group, matched non-trimetazidine users who were included in the main analysis were selected by greedy matching based on the PS. Non-trimetazidine users were matched to trimetazidine users in a ratio of 3:1 with a caliper of 0.2 times the standard deviation (SD) of the logit PS.

We used descriptive statistics to summarize the characteristics of the study population. Pearson's Chi-squared test and the Student's t-test were used for categorical and continuous variables, respectively, to compare baseline characteristics between trimetazidine users and matched non-trimetazidine users. The incidence rate per 1,000 person-years was calculated by dividing the number of parkinsonism events by the total number of person-years at risk and multiplying by 1,000. Accumulated person-years at risk were computed from the index date to either date of the event of parkinsonism, death, or the end of the study period (31 December 2015), whichever occurred first.

The risk of parkinsonism was assessed using univariate and multivariate Cox proportional hazard regression analyses to adjust the effects of demographic characteristics, comorbidities, and concurrent medications, and HRs and 95% CIs were estimated. The proportional hazard assumption was examined graphically using log (minus log) curves. Combined effects of trimetazidine with concurrent use of other parkinsonism-inducing drugs, were also evaluated by Cox proportional hazard modeling.

2.6. Sensitivity Analysis

Sensitivity analysis was conducted by shifting the index date from 1 January 2008 to 1 January 2007, 2009, or 2010. As the index date shifted, the "exposure ascertainment period" and "follow-up period" were changed accordingly, and the eligible populations, as well as variables related to exposure, outcome, comorbid diseases, and concurrent medications were also reassessed. Accordingly, any changes in the risk of parkinsonism were evaluated by calculating the aHRs. Moreover, an additional sensitivity analysis was performed by demonstrating the follow-up periods into two additional segments; within 1 year and from 1 to 8 years. The aHRs for trimetazidine were calculated based on newly captured the outcome variable according to the specific follow-up periods.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and the level of statistical significance was set at $p < 0.05$.

Chapter 3. Results

3.1. Demographic Characteristics of the Study Population

Of the eligible 656,524 patients in the study cohort, 9,712 trimetazidine users, and 29,116 PS-matched non-trimetazidine users were analyzed in this study. A flow chart depicting the selection procedure is shown in Figure 3.

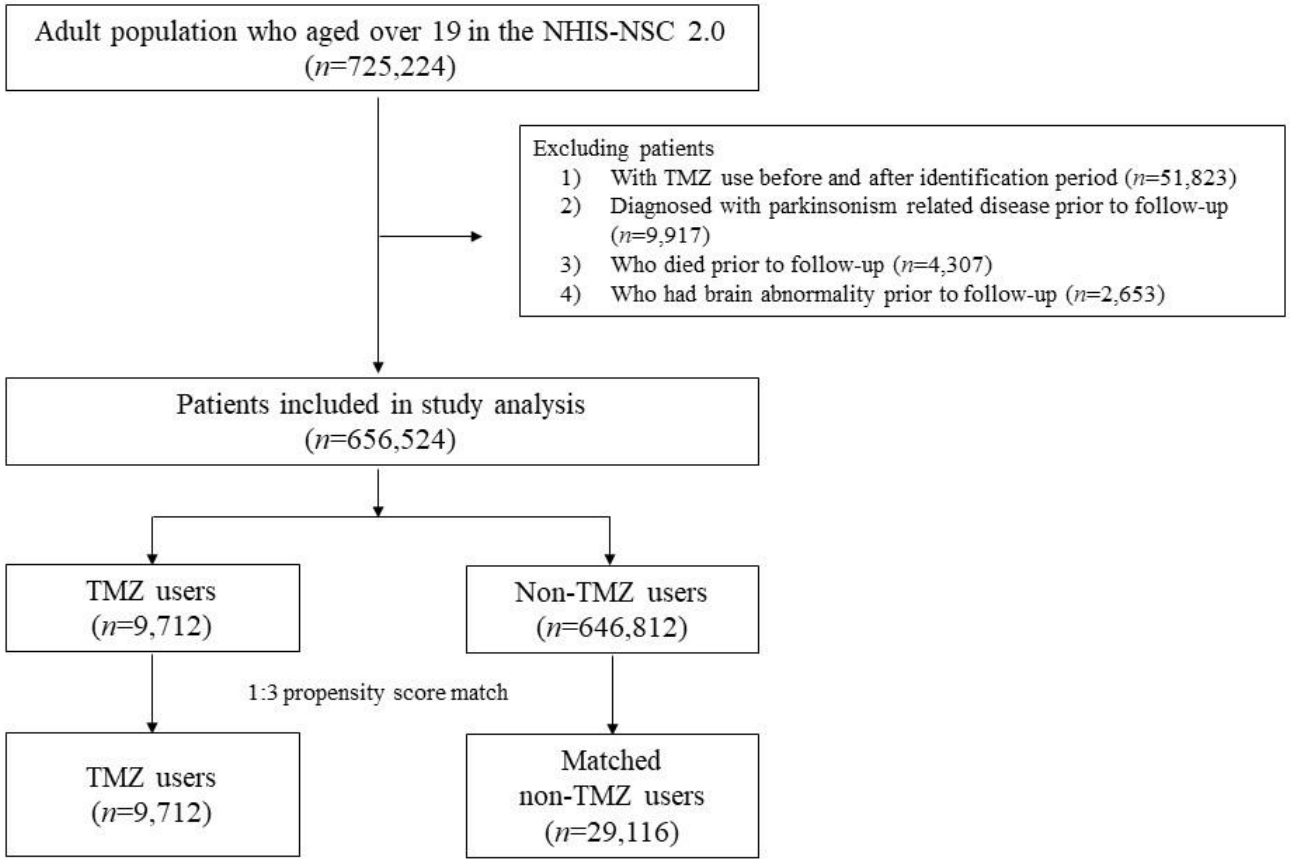

Figure 3. Flow chart of the study cohort. TMZ, trimetazidine.

The predictability of the constructed PS model was high, with a *c*-statistic of 0.81 (Appendix 1). The PS matching process resulted in similar PS distributions between trimetazidine users and non-trimetazidine users (Appendix 2).

Baseline demographic characteristics of the study population of trimetazidine users and matched non-trimetazidine users are shown in Table 4. The mean age (±SD) of the study population was 52.22 (±15.15) years, and women constituted 65.29%. About 44% of the study population lived in urban areas. Over half of the study population (55%) was diagnosed with hypertension and about one-third (30%) had ischemic heart disease diagnostic code. Regarding concurrent medications use, most of the study population (85%) used prokinetics, and about one-quarter (24%) had at least one or more prescription records of CCBs. The patterns of concurrent medications use except for dopamine depleters and prokinetics, and clinical comorbidities including hypertension, head injury, and liver disease were statistically different between the trimetazidine and non-trimetazidine users. No statistical differences were observed between trimetazidine and non-trimetazidine users with respect to age, sex, or area of residence.

Table 4. Demographic characteristics of the study population.

Characteristics	Total		Trimetazidine users		Matched non-Trimetazidine users		P-value*
	n=38,828	%	n=9,712	%	n=29,116	%	
Sex							0.31
Male	13,477	34.71	3,412	35.13	10,065	34.57	
Female	25,351	65.29	6,300	64.87	19,051	65.43	
Age							
Mean (SD)	52.22 (15.15)		51.98 (15.21)		52.30 (15.13)		0.08
Younger than 50 years	16,460	42.39	4,190	43.14	12,270	42.14	0.17
50-65 years	12,797	32.96	3,182	32.76	9,615	33.02	
65 years and older	9,571	24.65	2,340	24.09	7,231	24.84	
Insurance type							0.002
Health Insurance	35,622	91.74	8,835	90.97	26,787	92.00	
Medical Aid	3,206	8.26	877	9.03	2,329	8.00	
Area of residence							0.77
Capital city (Seoul)	6,088	15.68	1,509	15.54	4,579	15.73	
Metropolitan city	10,955	28.21	2,766	28.48	8,189	28.13	
Rural area	21,785	56.11	5,437	55.98	16,348	56.15	
Comorbidity							

Diabetes	14,334	36.92	3,554	36.59	10,780	37.02	0.45
End stage renal disease	140	0.36	41	0.42	99	0.34	0.25
Stroke	10,218	26.32	2,617	26.95	7,601	26.11	0.10
Dementia	89	0.23	27	0.28	62	0.21	0.26
Hypertension	21,423	55.17	5,241	53.96	16,182	55.58	0.006
Ischemic heart disease	11,817	30.43	2,981	30.69	8,836	30.35	0.52
Dyslipidemia	18,052	46.49	4,478	46.11	13,574	46.62	0.38
Head injury	1,208	3.11	342	3.52	866	2.97	0.008
Severe liver disease	572	1.47	164	1.69	408	1.40	0.04
Concurrent medication[†]							
Typical antipsychotics	2,746	7.07	738	7.60	2,008	6.90	0.02
Atypical antipsychotics	506	1.30	148	1.52	358	1.23	0.03
Prokinetics	32,901	84.74	8,172	84.14	24,729	84.93	0.06
Calcium channel blockers	9,178	23.64	2,369	24.39	6,809	23.39	0.04
Anti-epileptics	551	1.42	167	1.72	384	1.32	0.005
Dopamine depleters	5	0.01	2	0.02	3	0.01	0.60

Propensity score	0.95 (0.060)	0.95 (0.059)	0.70

*Pearson' s Chi-squared and Student' s t-test were used for comparing the categorical and continuous variables between trimetazidine users and matched non-trimetazidine users, respectively. The continuous variables in this table were the mean age and propensity score.
†The complete list of concurrent medications is shown in Table 3.
Abbreviation: SD, standard deviation.

3.2. The Risk of Parkinsonism associated with Trimetazidine Use

The proportional hazard assumption was checked and hold from log (minus log) curves (Appendix 3). No covariate showed any significant interaction with trimetazidine use by multivariate Cox proportional hazard regression modeling (Appendix 4).

A total of 2,084 parkinsonism events occurred during the observation period of 282,654 person-years, with an overall incidence rate of 7.37 per 1000 person-years. The incidence rate of parkinsonism was significantly higher in trimetazidine users than matched non-trimetazidine users (9.34 vs. 6.71 per 1,000 person-years, respectively; $p < 0.0001$), and trimetazidine use significantly increased the risk of parkinsonism (adjusted HR [aHR] = 1.38; 95% CI = 1.26-1.51). Being male and having Medical Aid insurance were associated with a reduced and an increased risk of parkinsonism, respectively. Compared to the population who were aged under 50 years, those aged over 50 years were more likely to develop parkinsonism (aHR = 2.48; 95% CI = 2.18-2.81 for age 50-64 years, and aHR = 3.22; 95% CI = 2.81-3.68 for age 65 years and older). Comorbidities including diabetes, ESRD, and stroke, and concurrent medications such as typical antipsychotics, atypical

antipsychotics, prokinetics, and CCBs were significant predictors of a new diagnosis of parkinsonism. Full model estimates are shown in Table 5.

Table 5. Incidence rates and hazard ratios of parkinsonism associated with trimetazidine use.

Characteristics	No. of subjects	Person-years	No. of events	Incidence rate*	Unadjusted HRs (95% CI)	P-value	†Adjusted HRs (95% CI)	P-value
All subjects	38,828	282,654	2,084	7.37				
Trimetazidine								
No	29,116	211,814	1,422	6.71	1.00 (reference)		1.00 (reference)	
Yes	9712	70,840	662	9.34	1.39 (1.27-1.53)	<0.0001	1.38 (1.26-1.51)	<0.0001
Sex								
Male	13,477	96,966	565	5.83	0.71 (0.65-0.78)	<0.0001	0.80 (0.73-0.88)	<0.0001
Female	25,351	185,689	1,519	8.18	1.00 (reference)		1.00 (reference)	
Age								
Younger than 50 years	16,460	128,910	394	3.06	1.00 (reference)		1.00 (reference)	
50-65 years	12,797	94,551	882	9.33	3.05 (2.71-3.44)	<0.0001	2.48 (2.18-2.81)	<0.0001
65 years and older	9571	59,293	808	13.63	4.43 (3.93-5.00)	<0.0001	3.22 (2.81-3.68)	<0.0001
Insurance type								
Health Insurance	35,622	262,283	1,759	6.71	1.00 (reference)		1.00 (reference)	
Medical Aid	3,206	20,372	325	15.95	2.37 (2.10-2.67)	<0.0001	1.79 (1.58-2.02)	<0.0001

Area of residence								
Capital city (Seoul)	6088	45,254	238	5.26	1.00 (reference)		1.00 (reference)	
Metropolitan city	10,955	80,524	548	6.81	1.29 (1.11–1.51)	0.001	1.33 (1.15–1.55)	0.0002
Rural area	21,785	156,877	1,298	8.27	1.57 (1.37–1.80)	<0.0001	1.42 (1.24–1.63)	<0.0001
Comorbidity								
Diabetes	14,334	99,587	1,043	10.47	1.84 (1.69–2.00)	<0.0001	1.20 (1.09–1.32)	0.0002
End stage renal disease	140	729	16	21.95	2.96 (1.81–4.84)	<0.0001	2.11 (1.28–3.46)	0.003
Stroke	10,218	69,204	806	11.65	1.94 (1.78–2.12)	<0.0001	1.20 (1.09–1.31)	0.0002
Dementia	89	495	7	14.15	1.90 (0.90–3.98)	0.26	0.67 (0.31–1.41)	0.29
Hypertension	21,423	149,341	1,462	9.79	2.09 (1.90–2.30)	<0.0001	1.04 (0.93–1.16)	0.55
Ischemic heart disease	11,817	81,946	850	10.37	1.68 (1.54–1.84)	<0.0001	1.09 (0.99–1.21)	0.07
Dyslipidemia	18,052	129,166	1,206	9.34	1.63 (1.50–1.78)	<0.0001	1.09 (0.99–1.21)	0.08
Head injury	1,208	8,453	88	10.41	1.43 (1.15–1.77)	0.001	1.23 (0.99–1.53)	0.06
Severe liver disease	572	3,682	39	10.59	1.44 (1.05–1.98)	0.02	1.14 (0.83–1.57)	0.42
Concurrent medication†								

Typical antipsychotics	2,746	18,574	266	14.32	2.08 (1.83−2.36)	<0.0001	1.66 (1.45−1.89)	<0.0001
Atypical antipsychotics	506	2,856	55	19.26	2.63 (2.01−3.44)	<0.0001	1.60 (1.21−2.10)	0.001
Prokinetics	32,901	238,121	1,916	8.05	2.13 (1.82−2.49)	<0.0001	1.56 (1.33−1.83)	<0.0001
Calcium channel blockers	9,178	65,308	663	10.15	1.55 (1.42−1.70)	<0.0001	1.22 (1.11−1.35)	<0.0001
Anti−epileptics	551	3,526	40	11.34	1.54 (1.13−2.11)	0.01	1.00 (0.73−1.38)	0.98
Dopamine depleters	5	35	1	28.93	3.93 (0.55−27.88)	0.17	1.83 (0.26−13.08)	0.55

*The incidence rates were presented on a basis of per 1,000 person−years.
†Adjusted hazard ratios (95% confidence intervals) were calculated with a multivariate Cox proportional hazard model for parkinsonism adjusting all covariates presented in this table.
‡The complete list of concurrent medications is shown in Table 3.
Abbreviations: CI, confidence interval; HR, hazard ratio; No, number.

3.3. The Cumulative Dose-response Relationship and Combined Effects with Other Parkinsonism-inducing Medications

Figure 4 shows the Kaplan-Meier curve for the cumulative incidence of parkinsonism. Cumulative incidence of parkinsonism showed an increasing trend with higher cumulative doses of trimetazidine, compared with non-trimetazidine use ($p < 0.001$).

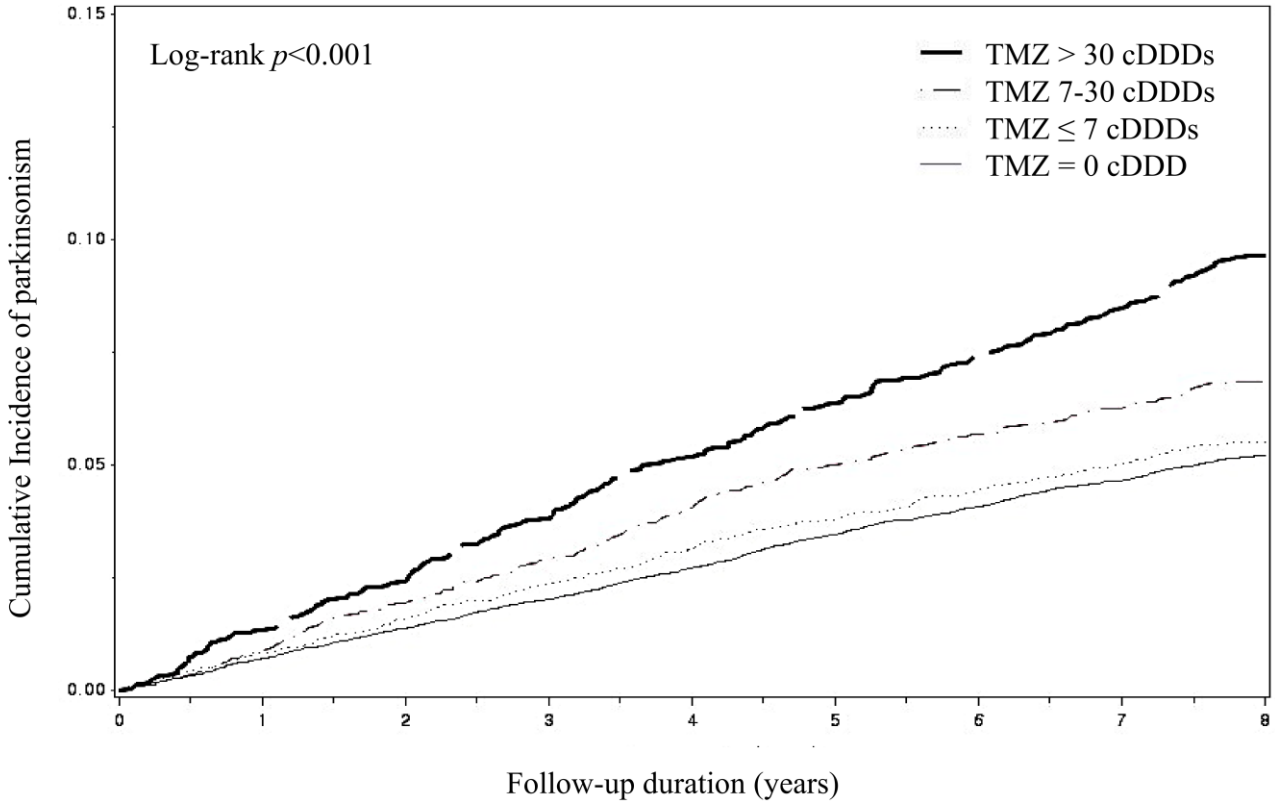

Figure 4. Kaplan-Meier curve with cumulative incidence of parkinsonism by cumulative defined daily doses (cDDDs) of trimetazidine use during follow-up period. TMZ, trimetazidine.

The combined effects of trimetazidine and concurrent medications, such as antipsychotics, prokinetics, CCBs, anti-epileptics, and dopamine depleters on the risk of parkinsonism are shown in Table 6. Trimetazidine users who were concurrently on those medications had a higher risk of parkinsonism than trimetazidine users who were not on other medications. The risk of parkinsonism increased as the number of concurrent medications increased (aHRs = 2.30, 2.96, and 4.58; 95% CIs = 1.80–2.93, 2.27–3.86, and 3.16–6.64 for one, two, and three concurrent medications, respectively, p for trend = 0.005).

Table 6. Combined effects for parkinsonism associated with trimetazidine use and inducing medications* (N=13,413).

Concurrent medications	No. of subjects	Person-years	No. of events	Incidence rate†	Unadjusted HRs (95% CI)	Adjusted HRs‡ (95% CI)	*p* for trend
None§	3,701	27,950	80	2.862	1.00 (reference)	1.00 (reference)	0.005
Trimetazidine only	1,224	9,206	45	4.888	1.71 (1.19-2.46)	1.70 (1.18-2.45)	
Trimetazidine + 1 parkinsonism inducing drug	5,760	42,381	356	8.400	2.93 (2.30-3.73)	2.30 (1.80-2.93)	
Trimetazidine + 2 parkinsonism inducing drugs	2,382	16,984	213	12.541	4.37 (3.38-5.65)	2.96 (2.27-3.86)	
Trimetazidine + 3 or more parkinsonism inducing drugs	346	2,269	48	21.152	7.32 (5.12-10.48)	4.58 (3.16-6.64)	

*Inducing medications included typical and atypical antipsychotics, calcium channel blockers, prokinetics, anti-epileptics, and dopamine depleters.
†The incidence rates were presented on a basis of per 1,000 person-years.
‡Adjusted hazard ratios (95% confidence intervals) were calculated with a multivariate Cox proportional hazard model for parkinsonism adjusting all covariates presented in Table 5.
§The study subjects who used one or more parkinsonism inducing drugs without trimetazidine were excluded from this analysis.
Abbreviations: CI, confidence interval; HR, hazard ratio; No, number.

3.4. Sensitivity Analysis

Sensitivity analysis showed that the risk of parkinsonism associated with trimetazidine use for each shifted index date remained higher compared with non-trimetazidine use (Table 7). Table 8 shows the aHRs of trimetazidine use for parkinsonism based on dividing the follow-up period. Similar to the overall risk on the 8-year follow-up period, the trimetazidine use significantly increased the risk of parkinsonism during the 1-year follow-up period.

Table 7. Adjusted hazard ratios of trimetazidine use for parkinsonism with shifting index date.

Index date	No. of subjects	Person-years	No. of events	Incidence rate*	Adjusted HRs of Trimetazidine use (95% CI) †	P-value
Shifting the index date, year, with respective eligible population and exposure ascertainment ‡						
January 1, 2007	4,989	40,538	377	9.30	1.43 (1.26-1.61)	<0.0001
January 1, 2008 (main)	9,712	70,840	662	9.35	1.38 (1.26-1.51)	<0.0001
January 1, 2009	14,253	92,061	844	9.17	1.35 (1.24-1.46)	<0.0001
January 1, 2010	18,787	105,032	969	9.23	1.37 (1.27-1.48)	<0.0001

*The incidence rates were presented on a basis of per 1,000 person-years.
†Adjusted hazard ratios (95% confidence intervals) of trimetazidine use were calculated with a multivariate Cox proportional hazard model for parkinsonism adjusting all covariates presented in Table 5.
‡Eligible population was re-assessed according to the shifted index date, and the trimetazidine exposure, as well as other covariates were re-measured from the time-stamped database, so that the predictive variables were measured prior to the outcome ascertainment period.
Abbreviations: CI, confidence interval; HR, hazard ratio; No, number.

Table 8. Adjusted hazard ratios of trimetazidine use for parkinsonism with different follow-up duration.

Follow-up duration	No. of events	Person-years	Incidence rate*	Adjusted HRs of Trimetazidine use (95% CI) †
Overall (8 years)	662	70,840	9.345	1.380 (1.258-1.514)
Within 1year	94	9,632	9.759	1.391 (1.088-1.778)
> 1 year	568	61,209	9.280	1.379 (1.248-1.523)

*The incidence rates were presented on a basis of per 1,000 person-years.
†Adjusted hazard ratios (95% confidence intervals) of trimetazidine use were calculated with a multivariate Cox proportional hazard model for parkinsonism adjusting all covariates presented in Table 5.

Chapter 4. Discussion

To the best of our knowledge, this is the first population-based cohort study with longitudinal follow-up demonstrating the association between trimetazidine use and increased risk of parkinsonism in the Korean population. It has been more than a decade since the safety issue for trimetazidine-associated parkinsonism was raised, but only a few studies conducted in European countries have reported the movement disorders related to trimetazidine. We recently reported a similar association between trimetazidine use and parkinsonism in a cross-sectional study using 1-year data [47]. Compared with our previous cross-sectional study, the present study has greater validity because we used a cohort study design and included a greater number of trimetazidine users (>9,000 patients). Moreover, the cumulative dose-response relationship between trimetazidine use and the risk of parkinsonism, as well as the combined effects of trimetazidine with other parkinsonism-inducing medications were also demonstrated using individual prescription records. In South Korea, there were no published pharmacovigilance studies that reported such cases with the adverse event or used the Korea Adverse Event Reporting System database. The paucity of the published studies reflects that

trimetazidine-associated parkinsonism is highly unrecognized and neglected by healthcare professionals in Europe and Asia including South Korea [26, 28, 32, 33, 42]. Therefore, the findings from our study using RWD derived from the general population could provide clinical relevance and insights on the occurrence of trimetazidine-associated parkinsonism, adding to existing knowledge regarding the risk of trimetazidine itself or in combination with other drugs. Furthermore, since the new usage of trimetazidine in various clinical conditions including contrast-induced nephropathy, heart failure, and peripheral artery disease has been studied and proposed [21-23], our study highlights that the consideration of weighing the parkinsonism risk and benefits is needed.

Our major findings indicated a significantly higher incidence rate and an increased risk of parkinsonism in trimetazidine users than those from non-trimetazidine users. Our result of the incidence rates could not be directly comparable as there were no published studies for providing the incidence rate of trimetazidine-associated parkinsonism on a person-year basis. However, it was lower than the incidence rate of parkinsonism by antipsychotics (as 38.8 per 1,000 person-years) [35] and comparable with the incidence rate by cinnarizine (as 8.36 per 1,000 person-year) [49]. The level of the association with trimetazidine in our study (aHR =

1.38) corroborates aOR reported from a cross-sectional evaluation using 1-year data (aOR = 1.39) [47]. Consistent with many previous studies, our regression results showed that antipsychotics and prokinetics had higher aHRs of parkinsonism than that with anti-epileptics and CCBs, which are considered intermediate risk drugs [29]. Although direct comparison of risks is inappropriate since the control group in our study is not other parkinsonism-inducing medications, the risk of parkinsonism may be lower with trimetazidine compared to high-risk drugs, such as antipsychotics and prokinetics, but higher with trimetazidine than intermediate risk drugs.

Of the various potential pathways of developing DIP [33, 38], a possible mechanism underlying trimetazidine-induced parkinsonism was suggested as blockade of post-synaptic dopamine D_2 The fact that piperazine core, commonly present in certain drugs, such as antipsychotics including chlorpromazine, clozapine and aripiprazole, cinnarizine, and flunarizine has an affinity to D_2 receptors was demonstrated in a number of both *in vivo* and *in vitro* studies. Subsequently, it is anticipated that trimetazidine, one of the piperazine derivatives might induce parkinsonism through a similar pathogenic mechanism [41, 55]. Since the affinity for D_2 receptors is dependent on the chemical structure of piperazine

ligands [41, 56] and may contribute to developing parkinsonism [49], further investigation into the affinities of receptors for trimetazidine and its metabolites to provide more accurate information on predicting its potential to induce parkinsonism is necessary.

In In the present study, we determined the cumulative dose-response relationship by analyzing all prescription claims data generated from both outpatient and inpatient encounters. To assess the cumulative trimetazidine exposure and its effect on the risk of parkinsonism, the DDD system validated by WHO Collaborating Center for Drug Statistics Methodology was applied [51] since this system has been suggested as a reliable tool used in many drug utilization studies [57, 58]. The incidence rate of parkinsonism showed an increasing trend with the cumulative dose of trimetazidine, from even the lower cumulative doses (≤7 cDDDs) of trimetazidine compared with no use of trimetazidine. This dose-response relationship has been similarly reported in previous studies of other drugs, such as flunarizine and zolpidem [49, 59]. An *in vitro* study suggested that the accumulation of metabolites [41] could be a potential explanation for the cumulative dose-response relationship of flunarizine. We believe that healthcare professionals should be aware of the cumulative dose effect of

trimetazidine on the risk of parkinsonism and should exercise caution when prescribing trimetazidine for an extended time.

Our study demonstrated the combined effect of trimetazidine with other parkinsonism-inducing drugs. Patients who used trimetazidine combined with three or more parkinsonism-inducing drugs showed almost twice the risk of parkinsonism than those who used trimetazidine plus one of these drugs. This finding has particular significance for older patients subjected to polypharmacy, as they are more frequently prescribed parkinsonism-inducing medications, including antipsychotics, prokinetics, and CCBs, to treat multiple chronic conditions and decreased physiological functioning [60, 61]. A study in older Korean patients found that, on average, more than three antipsychotic drugs were prescribed concurrently in psychiatric outpatient settings [62]. Since age is also considered an obvious risk factor for parkinsonism [28], closer monitoring of older patients for DIP is essential.

The literature indicated that trimetazidine-associated parkinsonism impacted patients' quality of life and was poorly responsive to clinical treatment with levodopa or dopamine agonists due to the pathogenic mechanisms of DIP [42]. As DIP is a mostly reversible condition and withdrawal of the offending drugs improved the parkinsonism condition, early recognition and prompt

discontinuation of such drugs can be crucial for the management of parkinsonism. However, trimetazidine has not been well documented as a parkinsonism-inducing medication in previous DIP-related studies [26, 27, 29, 32, 48]. Unlike cinnarizine and flunarizine as antivertigo agents which have been identified and presented as high- to intermediate-risk drugs in several studies [28, 29, 32], trimetazidine has relatively not been considered as an offending drug of parkinsonism, despite showing the comparable risk of parkinsonism. Moreover, our results showed that trimetazidine and CCBs, i.e. cinnarizine and flunarizine were used with similar frequency, but trimetazidine was not even mentioned from the recent DIP-related epidemiology studies conducted in South Korea [26, 28, 32]. Therefore, we believe that our study, demonstrating the significant risk of trimetazidine-associated parkinsonism, will help to raise awareness of trimetazidine-associated parkinsonism and the importance of recognizing DIP. Furthermore, the important role of healthcare professionals, especially the role of pharmacists, should be highlighted by enabling them to perform closer monitoring of clinical symptoms related to the development and aggravation of parkinsonism through timely and comprehensive medication reviews and to make appropriate referrals to clinicians when DIP related safety concerns are

identified.

Even after the indication for trimetazidine was restricted due to safety issues, many physicians still prescribed trimetazidine for vertigo and tinnitus off-label, and they were not aware of the latest safety information regarding trimetazidine [63]. Besides, it was reported in our previous cross-sectional study [47] that part of trimetazidine users was diagnosed with movement disorder prior to prescription of the trimetazidine despite contraindication of trimetazidine use in the patients with PD or movement disorders. Since the clinical benefits of discontinuation of trimetazidine in parkinsonism were proved with remarkable improvement of movement symptoms as well as the quality of life [64], we believe that future research is required on the current status of discontinuation on trimetazidine use after DIP diagnosis in South Korea to emphasize the clinical rationale for trimetazidine withdrawal or avoidance.

There are some limitations to this study. First, the diagnosis of parkinsonism in our study population was identified via ICD-10 codes taken from the claims database. This could be inaccurate or incomplete because an accurate diagnosis of trimetazidine-induced parkinsonism should be based on imaging investigation, together with the demonstrable improvement of clinical features upon

trimetazidine discontinuation [42]. In addition, data on the potential confounders of parkinsonism [29], including genetic factors, toxic substances, certain infectious diseases, and lifestyle factors as physical activity level, could not be obtained from the claims database. Second, there could have been selection bias when identifying non-trimetazidine users from NHIS-NSC 2.0. To minimize this bias, we used a PS-matching process, and a similar PS distribution between trimetazidine user and non-user group after matching was confirmed. The baseline characteristics, except for some comorbid conditions and concurrent medications, showed no significant differences between trimetazidine users and non-trimetazidine users. While the PS has become one of the most popular tools for adjusting the confounders in the RWD analyses, one could consider utilizing an active comparator, or negative/positive control outcomes to demonstrate the presence or magnitude of the potential selection bias [5]. Using the active comparator can mitigate the differences in baseline characteristics, especially disease severity between the study groups. Also, identifying known associations or lack of associations correctly by setting the control outcomes can be a great tool for confirming the validity of study analyses. Although our study has a weakness of not evaluating the selection bias extensively and rigorously using

the various methodological tools mentioned above, we adjusted various confounders related to parkinsonism by in the design stage and the analysis stage using matching method and multivariate regression analysis, respectively. Third, treatment duration or cumulative doses of other concurrent medications were not considered in our analysis. Since both the duration and the dose of the offending medication are possible risk factors for developing DIP [29, 35, 49, 59], further analyses are needed. Fourth, there could be possible misclassification bias of confounders, especially in cases where patients started medications or disease with documented risks of DIP after the index date. However, to address this issue, we performed the sensitivity analyses by shifting the index date backward and forward to check possible confounding, which resulted in only minor changes in the aHRs. Fifth, our study evaluated the combined effect of trimetazidine with other medications by regarding the patients who used parkinsonism-inducing medications at least once in the 'exposure identification period' as concurrent medication users. Therefore, the precise additive effects of parkinsonism-inducing medications simultaneously use with trimetazidine by strict operational definitions for concurrent medications through identifying the overlap in the duration of medications should be evaluated in further

research. Lastly, since our study defined the exposure variable as one or more new prescriptions of trimetazidine and calculated the cumulative use of trimetazidine only in the 'identification period', we did not confirm the active use of trimetazidine until the outcome occurs. Since our study had an 8-year follow-up period, parkinsonism with delayed occurrence after the trimetazidine discontinuation can be included as an outcome. Although our additional sensitivity analysis also showed the increased risk of trimetazidine from the short follow-up period, the overall risk of trimetazidine for parkinsonism could be overestimated and the effect of cumulative dose on parkinsonism has to be cautiously interpreted. We believe additional comparative evaluations are needed in the future to better understand the risk of parkinsonism with other populations as the patterns of drug use, regulatory requirements, or treatment guidelines might differ by country.

Chapter 5. Conclusion

This is the first population-based longitudinal cohort study identifying the risk of trimetazidine-associated parkinsonism in the Korean population. The study findings indicated that trimetazidine use was associated with an increased risk of parkinsonism. Increased risks were observed with accumulated doses of trimetazidine, as well as concurrent use of other parkinsonism-inducing medications. The new usage of trimetazidine in various clinical conditions such as heart failure, and contrast-induced nephropathy has been proposed recently, but trimetazidine-associated parkinsonism was still unrecognized in the literature, as well as in the clinical situation. Our study highlights the need for increased awareness of trimetazidine-associated parkinsonism and the importance of closer monitoring, especially in older patients who may be predisposed to high cumulative doses of trimetazidine concurrently with other parkinsonism-inducing medications.

Generating RWE which can be applied to the clinical practice through the pharmacovigilance study using RWD is important in terms of safe drug use, especially for drugs with limited safety information. As this study was conducted using national health claim data which is one of the RWD provided by the government, we

believed that our study findings derived from the general Korean population could provide clinical relevance and insights on the safety problems, adding to the existing knowledge.

* This work is published in International journal of environmental research and public health [65].

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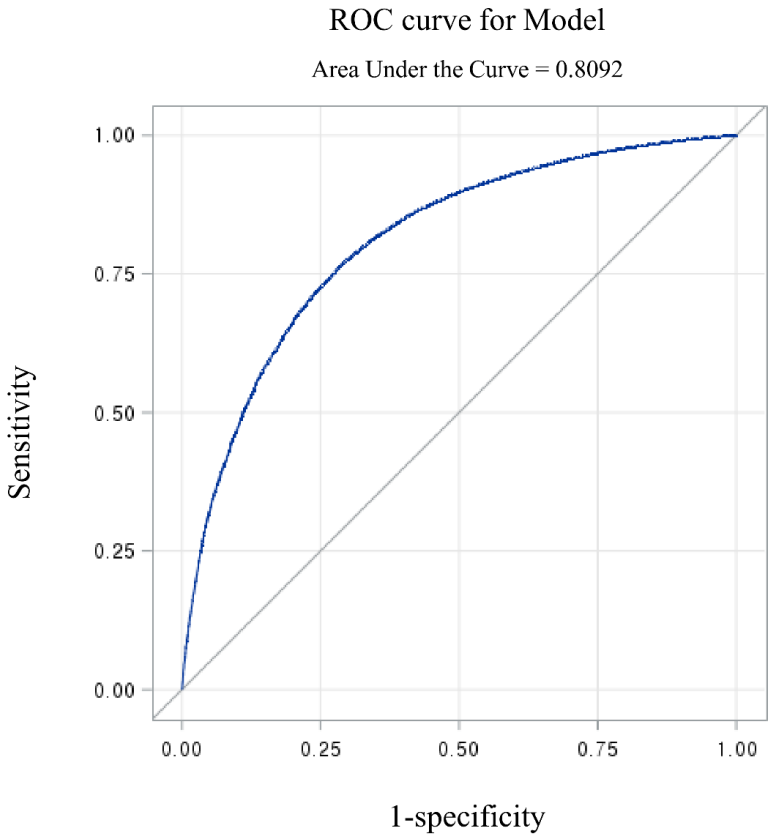
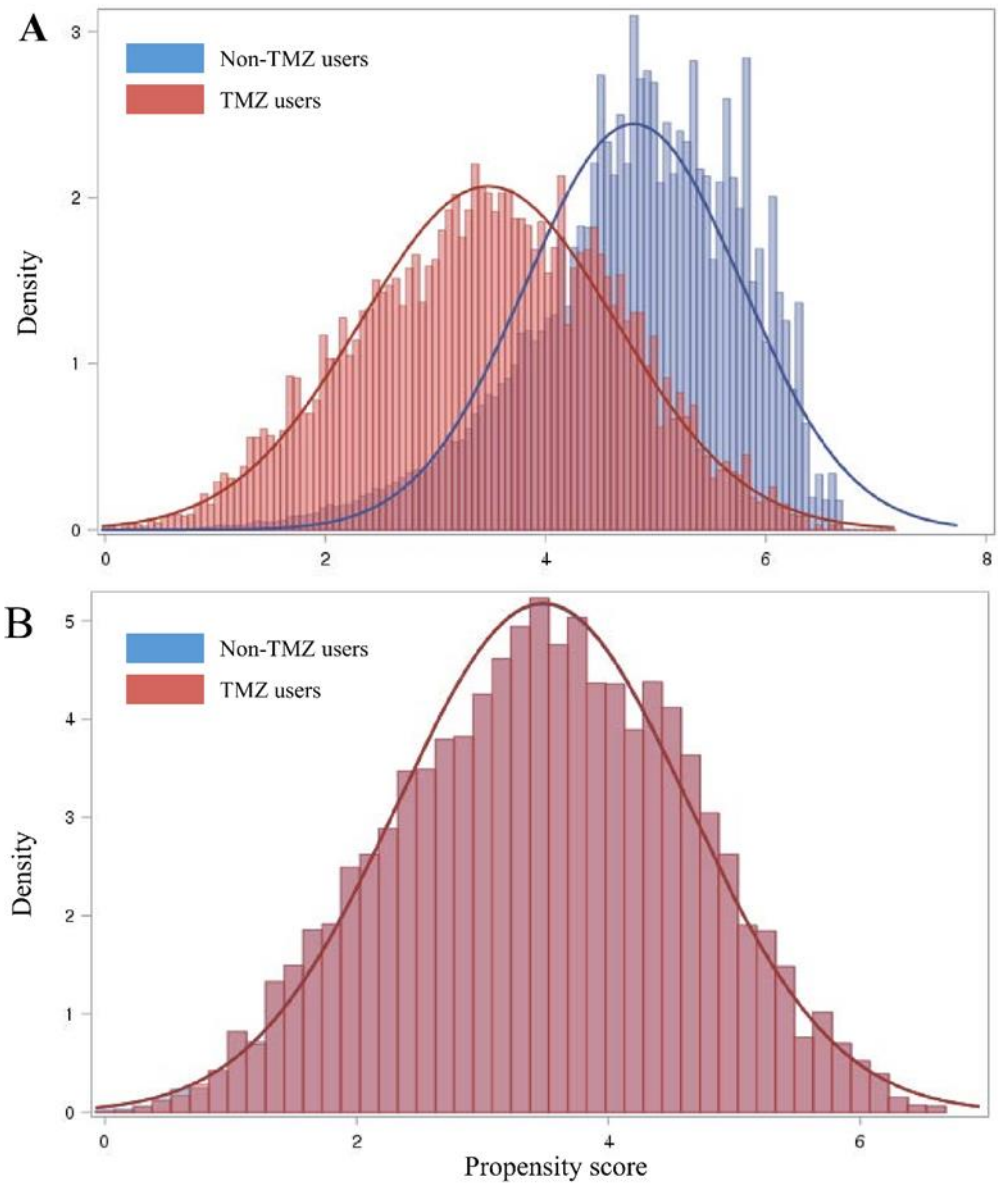
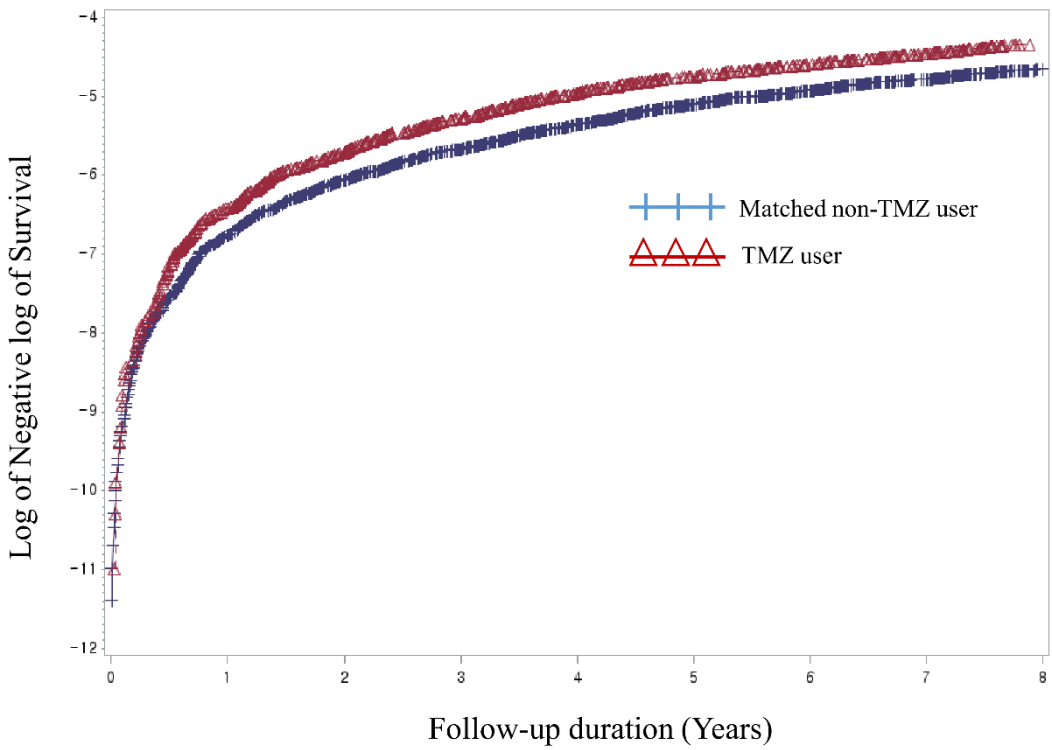
Appendix



Appendix 1. Receiver operating characteristics (ROC) curve for the propensity score model.



Appendix 2. Distribution of propensity score between trimetazidine users and non-trimetazidine users before (2a) and after (2b) propensity score matching. TMZ, trimetazidine.



Appendix 3. Log (minus log) curves for checking proportional hazard assumption. TMZ, trimetazidine.

Appendix 4. P-values for the interaction terms in the multivariate Cox proportional hazard regression model between trimetazidine use and covariates.

Variables*	P-value
Sex	0.50
Age	0.88
Public Insurance Scheme	0.58
Residency	0.20
Diabetes	0.64
ESRD	0.40
Stroke	0.81
Calcium channel blockers	0.83
Prokinetics	0.98
Typical antipsychotics	0.98
Atypical antipsychotics	0.28
Anti-epileptics	0.95

*These variables were the covariates with the multivariate Cox regression model p-value <0.05 in Table 5.

국문초록

다양한 real-world data (RWD)가 대두되고 빅데이터 활용이 전 세계적으로 상당한 관심을 받기 시작한 이래로, RWD 분석을 통해 생성된 real-world evidence가 전통적인 임상시험의 한계점을 보완하기 위해 생성되기 시작했다. 현재까지 RWD는 약물의 안전성을 모니터링하기위한 시판 후 감시에서 중요한 도구로 활용되고 있다. 우리나라는 국민건강보험이라는 단일 국가보험 체계가 마련되어 있어 건강보험 청구자료를 국가에서 체계적으로 수집하고 관리하고 있으며, 다양한 임상 환경 및 연구에서 활용될 수 있도록 전 국민을 대표하는 표본이 포함된 RWD를 제공하고 있다. 트리메타지딘(Trimetazidine)은 한국을 비롯한 여러 아시아 국가와 유럽에서 사용되고 있는 항 협심증 약제 중 하나로, 비교적 안전한 약제로 여겨졌으나 운동실조, 파킨슨병과 같은 운동장애 부작용 사례들이 보고되기 시작하였다. 드물지만 심각한 부작용인 운동장애가 지속해서 보고됨에 따라 유럽의약청(European Medicines Agency)에서는 트리메타지딘의 효과 및 안전성을 재평가하였고, 그에 따라 파킨슨씨병 환자에서는 트리메타지딘 사용이 금기되었다. 트리메타지딘은 미국 식품의약품안전처의 허가를 받지 않았기 때문에 최신의 약물 안전성 정보에 대한 접근이 제한적이었으며, 또한 트리메타지딘 관련 파킨슨증의 증거는 대부분 사례보고 연구나 소규모 관찰 연구에 의존되었고 그 위험 수준을 정량적으로 평가하기 위한 대규모 인구 기반 연구는 매우 드물다.

따라서 본 연구는 국민건강보험공단의 청구자료를 활용하여 트리메타지딘 사용과 파킨슨증의 발생 위험에 대하여 평가하고자 하였다.

본 연구는 국민건강보험공단에서 제공하는 14년의 종단데이터인 표본코호트 2.0 DB(National Health Insurance Service—National Sample Cohort 2.0)를 활용한 성향점수 매칭 코호트 연구로 19세 이상의 성인을 대상으로 하였다. 2008년 1월 1일을 기준일로 설정하여 이전 6년 동안엔 교란변수를 포함한 노출변수를 확인하였으며, 이후 8년은 결과변수를 확인하기 위한 추적기간으로 설정하였다. 트리메타지딘을 새롭게 사용하는 사람만을 식별하였으며, 트리메타지딘 비사용자는 성향점수 기반의 greedy matching 방법을 통해 트리메타지딘 사용자와 1 : 3 비율로 매칭되었다. 연구 결과변수는 추적관찰 기간 동안에 새롭게 발생한 파킨슨증이며, 교란변수로는 성별, 연령 등의 인구사회학적 특성, 파킨슨증 발생에 영향을 미치는 병존질환 및 병용약물이 포함되었다. 트리메타지딘 사용으로 인한 파킨슨증의 위험은 단변수 및 다변수 Cox 비례 위험 회귀분석을 사용하여 평가하였으며, 결과는 위험비(HRs)과 95% 신뢰구간으로 제시되었다. 또한 트리메타지딘 누적용량을 계산하여 파킨슨증의 발생 위험을 평가하였으며 트리메타지딘과 다른 위험약제와의 병용 효과를 Cox 비례 위험 회귀분석을 사용하여 평가하였다.

총 9,712명의 트리메타지딘 사용자와 29,116 명의 트리메타지딘 비사용자가 최종 분석에 포함되었다. 파킨슨증 발생률은 트리메타지딘 사용군에서 비사용군에 비해 유의하게 높았으며 (각 1,000 인년 당

6.71 vs 6.71; p <0.0001), 트리메타지딘의 사용은 파킨슨증의 발생 위험을 유의하게 증가시켰다 (aHR = 1.38; 95% CI = 1.26–1.51). 파킨슨증의 누적 발생률은 트리메타지딘의 누적 용량이 증가함에 따라 더 높게 나타났다 (p <0.001). 병용 효과의 경우, 트리메타지딘만 복용한 것에 비해 다른 위험 약제를 병용한 경우 위험도가 더 높게 나타났으며, 병용약제 수가 증가할수록 위험도가 선형적으로 증가하는 경향이 확인되었다 (p for trend = 0.005).

본 연구는 한국에서 트리메타지딘 사용에 따른 파킨슨증 발생 위험을 국가 수준의 건강보험 청구자료를 활용하여 인구기반으로 분석한 최초의 코호트 연구이다. 연구 결과에 따르면 트리메타지딘 사용은 파킨슨증의 위험을 증가시키며, 이러한 위험은 트리메타지딘의 누적 용량이 증가할수록, 위험 약제의 병용이 증가할수록 증가하는 것으로 나타났다. 본 연구의 결과는 실제 임상 환경에서 트리메타지딘을 사용하는 경우, 특히 장기적으로 사용하거나 다른 위험 약제를 병용할 가능성이 큰 노인에서 사용하는 경우 파킨슨증의 발생에 대한 면밀한 모니터링이 필요하다는 것의 근거로 활용될 수 있을 것이라 기대한다.

* 본 내용의 일부는 International journal of environmental research and public health 학술지에 출판되었음 [65].

주요어 : 트리메타지딘, 약물 유발 파킨슨증, 협심증 치료제, 건강보험 청구자료

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