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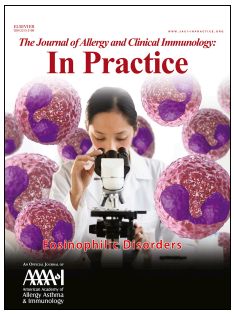

Cost-effectiveness of tiotropium in elderly patients with severe asthma using real-world data

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Original article

Cost-effectiveness of tiotropium in elderly patients with severe asthma using real-world data

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Abstract

Background

Tiotropium has the potential to alleviate asthmatic symptoms caused by the aging of lungs. However, few studies have focused on specific treatments for elderly asthma patients.

Objectives

This study aimed to estimate the cost-effectiveness of adding tiotropium to inhaled corticosteroids and long-acting beta-agonists (ICS/LABA) in elderly severe asthma patients using real-world data.

Methods

Phase I was a retrospective cohort study using the National Health Insurance claims data to measure clinical and economic outcomes. In phase II, a Markov model was constructed to evaluate cost-effectiveness from Korean healthcare system perspective, based on phase I, including two health states and an asthma exacerbation event. We estimated cost given in 2018 US dollars, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER). Subgroup analyses for poorly controlled asthma patients (frequent short-acting beta-agonist (SABA) users; frequent exacerbators) were performed.

Results

In elderly severe asthma patients, the incremental cost and effectiveness in the tiotropium group compared to the ICS/LABA group were $2,281 and 0.038 QALYs, respectively. The ICER was $60,074/QALY, indicating that the addition of tiotropium is not a cost-effective alternative. Meanwhile, two subgroups with poorly controlled asthma showed that adding tiotropium is a cost-effective alternative (frequent SABA users $4,078/QALY; frequent exacerbators $8,332/QALY).

Conclusion

Tiotropium shows a higher cost-effectiveness profile when applied to elderly patients with uncontrolled symptoms. These results using real-world evidence provide information beyond the clinical outcomes reported by randomized clinical trials, providing a complementary ground in establishing the reimbursement criteria of tiotropium for elderly patients with severe asthma.

Highlights box:

What is already known about this topic?

Adding tiotropium to the standard of care for severe asthma patients showed significant improvements in preventing asthma exacerbations in adults.

What does this article add to our knowledge?

In elderly patients with severe asthma, adding tiotropium resulted in a significant decrease in asthma exacerbation rates. In particular, it shows a higher cost-effectiveness profile when applied to elderly patients whose symptoms are poorly controlled.

How does this study impact current management guidelines?

Our results provide information on the treatment effect of tiotropium targeting elderly patients who are usually excluded from RCTs, thus, offering a basis for establishing reimbursement criteria for tiotropium for elderly patients with severe asthma.

Keywords:

Asthma; Muscarinic Antagonists; Tiotropium; Elderly patients; Asthma exacerbation; Retrospective studies; Real-world data; Cost-effectiveness analysis; Pharmacoeconomics; Incremental cost-effectiveness ratio

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Abbreviations:

COPD, Chronic obstructive pulmonary disease

ED, Emergency department

GINA, Global Initiative for Asthma

HIRA, The Health Insurance Review and Assessment Service

ICER, Incremental cost-effectiveness ratio

ICS, Inhaled corticosteroid

LABA, Long-acting beta-agonist

LAMA, Long-acting muscarinic antagonists

NHI, National Health Insurance

OCS, Oral corticosteroids

QALY, Quality-adjusted life year

RCTs, Randomized clinical trials

RWD, Real-world data

RWE, Real-world evidence

SABA, Short-acting beta-agonist

SCS, Systemic corticosteroid

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Introduction

Asthma is one of the most common chronic airway diseases, defined by various respiratory symptoms due to reversible airflow limitation.[1, 2] Approximately 300 million people worldwide have asthma, with 250,000 deaths annually ascribed to the disease.[3] Although there is a common belief that asthma occurs in childhood and subsequently resolves, several studies show that a significant number of relatively older people develop asthma that persists throughout their lifespan.[4, 5] With the aging global population, the number of the elderly with asthma is expected to increase.[6, 7]

An inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) combination therapy is recommended as the gold standard for asthma.[1] However, it showed a significant therapeutic effect in controlling asthma symptoms in only about 70% of asthma patients.[8] This unmet need in asthma treatments leads to long-acting muscarinic antagonists (LAMA) treatment, the traditional gold standard for chronic obstructive pulmonary disease (COPD). Randomized clinical trials (RCTs) that compared the outcomes of adding tiotropium, a kind of LAMA, to ICS/LABA for asthma patients have shown significant improvements in pulmonary function and exacerbation rates.[9] Consequently, tiotropium has been approved for children and adults with poorly controlled asthma. According to the Global Initiative for Asthma (GINA) guideline, it is currently considered a preferred add-on controller to ICS/LABA for step five and an alternative add-on controller to high-dose ICS for step four.[1] Tiotropium inhibits the action of acetylcholine and results in a strong bronchodilation cascade.[10] It leads to an excellent effect against airway constriction and mucus hypersecretion due to inflammation.[11] As the mode of action of tiotropium is expected to relieve the symptoms that attribute to anatomical aging in the elderly's lungs; several studies have mentioned potential values in the treatment of elderly patients with severe asthma.[12]

Research using real-world data (RWD) is useful for studies targeting specific populations, such as the elderly, and can reflect prescription and medical usage patterns in practice.[13] RWD contains a wealth of information already collected in the clinical environment so that large and long-term data on the population of interest can be captured. To the best of our knowledge, no studies of tiotropium have targeted the elderly specifically, as they are usually excluded from RCTs due to comorbidities and

multiple drug use. Additionally, for the optimal allocation of health resources for an increasingly elderly population, cost-effectiveness analysis at a subdivided level, targeting a more specific population, is necessary. Therefore, we aimed to determine the cost-effectiveness of adding tiotropium to ICS/LABA for elderly patients with severe asthma and sub-specified groups using RWD that provides information beyond clinical results reported by RCTs. Our study results provide information regarding a more cost-effective alternative to treating elderly patients with severe asthma.

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Methods

Figure 1 depicts the two phases of our study. Phase Ⅰ was a retrospective cohort study using the South Korean National Health Insurance (NHI) claims data to generate real-world evidence (RWE). This study aimed to measure the clinical outcomes and costs of adding tiotropium to ICS/LABA for elderly patients with severe asthma. Phase II sought to establish the cost-effectiveness profile of adding tiotropium to ICS/LABA based on the results of phase Ⅰ.

Phase Ⅰ: Real-world evidence generation

In phase I, we utilized data documented between January 1, 2015 and June 30, 2018, in the NHI claims database obtained from the Health Insurance Review and Assessment Service (HIRA) of South Korea (Study ID: M20190224578).[14] The Institutional Review Board of Sungkyunkwan University approved our phase I study (approval number: SKKU-2017-05-002).

Our target population included elderly patients with severe asthma. Based on the GINA guidelines and local reimbursement guidelines, patients treated with tiotropium combined with ICS/LABA were selected as the tiotropium group. As a comparator, the ICS/LABA group, the patients treated with medium-high-dose ICS/LABA only were recruited. We used matching and weighting methods with the propensity score to limit to the severe asthma patients since medium-dose ICS/LABA can be used for a moderate population (weighted results were summarized in Table E2 and E3). They were also limited to those who experienced one or more severe asthma exacerbations despite persistently receiving medium-high-dose ICS/LABA. We constructed a cohort of elderly patients with severe asthma that satisfied the above criteria during the cohort enrollment period from January 1, 2016, to June 30, 2017. The list of medium-high-dose ICS/LABA combinations (Table E1) and detailed inclusion and exclusion criteria are described in an online repository.

We set the first prescription of tiotropium or ICS/LABA with asthma diagnosis as the tiotropium and ICS/LABA group's index date, respectively (Figure 1). The pre-index period was defined as 12 months before the index date and was used to obtain data on demographic characteristics,

158 comorbidities, comedications, and healthcare utilization of patients. Patients were followed up for a
159 year after the index date to obtain clinical outcomes and costs that would be utilized in phase II.

160 The clinical outcomes were the rate of asthma exacerbations separated into three different types
161 according to medical resources incurred by the treatment severity: systemic corticosteroid (SCS) burst,
162 emergency department (ED) visit, and hospitalization.[15, 16] An SCS burst was defined as an outpatient
163 visit with at least three days of high-dose oral corticosteroids (OCS) or a single SCS injection
164 accompanied by asthma diagnosis. An ED visit or hospitalization was limited to events with a medical
165 record of SCS burst to ensure an asthma-related event. An event of an ED visit followed by
166 hospitalization was classified as hospitalization, not as an ED visit. High-dose OCS was defined as a
167 medication equivalent to 30 mg prednisolone per day.[1] Costs were calculated for five items: two
168 controlled states for each group and three asthma exacerbations. Of the medical claims in the follow-
169 up period, only claims with asthma-related medication or tests with an asthma diagnosis were used to
170 estimate asthma-related costs.

171 Subgroup analyses were performed on two criteria as surrogate indicators for poorly controlled
172 symptoms. That is, whether the patients were prescribed short-acting beta-agonists (SABAs) four
173 times or more during the pre-index period (the frequent SABA users) and whether the patients
174 experienced asthma exacerbations two or more times during the pre-index period (frequent
175 exacerbators).

176 We used propensity score-based matching with a greedy matching algorithm to control for
177 potential confounding variables.[17] The incidence rate was calculated by dividing the total number of
178 asthma exacerbations observed in each group by the observation period (in person-years) to obtain the
179 clinical outcome. The rate ratio was calculated using Poisson regression, with 95% CI for statistical
180 significance. All data handling and statistical analyses were performed using SAS Software 9.4 (Cary,
181 NC).

182

183 Phase Ⅱ: A cost-effectiveness analysis

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The cost-effectiveness analysis targeted elderly patients with severe asthma, eligible for reimbursement upon receiving tiotropium in Korea (as with phase I), and compared ICS/LABA alone to ICS/LABA with tiotropium. The mean age and sex ratio from phase I were used as model input parameters (Table 1). We employed the Markov model over a lifetime horizon,[18, 19] with two health states (asthma-controlled and death) and an event including three types of asthma exacerbation (SCS burst, asthma-related ED visit, and asthma-related hospitalization) (Figure 1). The asthma-controlled state is where the patient's asthma symptoms are stable as a result of regular follow-up visits and controlled medication use. In this state, three types of exacerbation events may occur, defined as in phase Ⅰ. Death can occur within both the asthma-controlled state and during asthma exacerbation events, with different mortality rates. Asthma exacerbations were considered a possible event since they occur repeatedly but are also managed back to the control state with appropriate treatment. Based on the duration of treatment to return to the control state after an asthma exacerbation,[20] the cycle length was determined as two weeks. The analysis was performed from the healthcare system perspective, and both clinical outcomes and costs were discounted at a rate of 5% yearly. Microsoft Excel 2010 was utilized for the model.

The transition probabilities from the controlled state to exacerbation events were obtained by converting the incidence rates of asthma exacerbations in phase I (Table 1) using the formula derived from Briggs et al.[21] Deaths occurring after asthma exacerbations were considered asthma-related mortalities, applied from the study by Lee et al.[22] They reported a 0.21% mortality rate for patients who visited the ED, regardless of being hospitalized afterward, due to asthma in Korea (Table 1). We applied this value to the mortality rate of ED visits and hospitalization equally. All-cause mortality was defined to occur in the controlled state and assumed to be equal to Korea's standard mortality rate. Annual mortality rates presented in the life table were converted to such per two weeks, depending on age (Table E6).

The utility weight of the controlled state was obtained from Willson et al. (2014), in which the asthma-related quality of life was applied using EQ-5D collected from the PrimoTinA-asthma that included three states: controlled, partly controlled, and uncontrolled.[23] We have integrated utility

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weight to suit our study by considering the distribution of patients across model health states at baseline. Consequently, the utility weight in the controlled state was 0.753 for tiotropium and 0.752 for the ICS/LABA group, respectively (Table 1). The utility weight of an asthma exacerbation event was applied based on Lloyd et al.'s findings, targeting patients who corresponded to level 4 or 5 in the GINA guidelines.[24] They showed that the utility weight using EQ-5D in exacerbation events with oral steroids and hospitalization were 0.57 and 0.33, respectively (Table 1). The value for an ED visit was assumed to be the average of those with oral steroids and hospitalization (0.45).

Medical costs were derived from phase Ⅰ that used the gross-costing method. The controlled state costs for the two groups were calculated by converting annual costs into costs per model cycle. The treatment costs for the three types of exacerbations were applied as costs per exacerbation event calculated in phase I (Table E7).

The cost-effectiveness analysis results were represented by incremental cost-effectiveness ratio (ICER), an indicator of incremental cost on additional quality-adjusted life year (QALY) gained by adding tiotropium to ICS/LABA. The cost-effectiveness profile of tiotropium was set on the basis of the willingness-to-pay threshold of $20,979/QALY.[25] To confirm the robustness of this RWD approach, we compared the ICER calculated using clinical outcomes reported from the RCT of tiotropium with the base case. Additionally, we performed two subgroup analyses targeting frequent SABA users and frequent exacerbators. To identify the impact of changing key model inputs such as discount rates, time horizon, utilities of asthma exacerbation, the mortality rate due to hospitalization, or costs, a univariate sensitivity analysis was performed with plausible extremes based on available evidence.[26] The univariate sensitivity analysis results were summarized in the tornado diagram (Figure 2).

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Results

Clinical and economic outcomes from real-world data

We identified 4,738 elderly patients with severe asthma, consisting of 286 and 4,452 patients in the tiotropium and ICS/LABA groups, respectively (Figure E1). Among a total of 4,738 elderly patients with severe asthma, 274 and 822 patients were matched for the tiotropium and ICS/LABA groups, respectively. Table 2 shows the patients' baseline characteristics before and after propensity score matching (the same tables regarding each subgroup are shown in Tables E4 and E5). After matching, the balance between the covariates in the two groups improved considerably. However, there were still covariates with standardized mean differences greater than 0.1, such as anxiety, diabetes (complicated), and the proportion of patients who used SABA more than four times during the pre-index period. These were included in the Poisson regression model as a confounder in calculating the rate ratio. The c-statistics of the model and the p-value from Hosmer-Leme show goodness-of-fit test showed a proper calibration and fit for the propensity score model.

In the total population, the annual incidence rates of asthma exacerbation in the tiotropium and ICS/LABA groups were 1.55 (standard deviations: 4.33) and 2.09 (4.67), respectively (Table 3). The adjusted rate ratio (RR) of the incidence rates between the two groups was 0.72 (95% CI: 0.62–0.83). The incidence rate of SCS burst and ED visits in the tiotropium group was lower than that in the ICS/LABA group, but that of hospitalization in the tiotropium group was higher than that in the ICS/LABA group. In the subgroup analysis, the RR of the incidence rate of frequent SABA users and frequent exacerbators were 0.68 (0.60–0.85) and 0.77 (0.65–0.88), respectively. Asthma-related cost for the controlled state and asthma exacerbations in the total population and the two subgroups are shown in Table E7.

Cost-effectiveness outcomes

Regarding the base-case analysis, the average number of asthma exacerbations that an elderly patient in the tiotropium group would be expected to experience in their lifetime for SCS burst, ED visit, and hospitalization were 11.31, 0.09, and 2.70, respectively (Table 4). For patients in the

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ICS/LABA group, averages of 17.13, 0.19, and 2.16 were expected for SCS burst, ED visit, and hospitalization, respectively. There was a gain of 0.038 in the tiotropium group compared to the ICS/LABA group regarding the QALY. The lifetime cost for patients in the controlled state in the tiotropium group was estimated to be $9,907, about $1,638 more than that of the ICS/LABA group, and the treatment cost for asthma exacerbations was calculated to be $5,673, about $643 higher in the tiotropium group than in the ICS/LABA group. Thus, the total lifetime costs in the tiotropium and ICS/LABA groups were $15,580 and $13,299, respectively, the former being higher by $2,281 due to the high hospitalization rate. Consequently, the ICER was calculated at $60,074; hence, the additional use of tiotropium was a non-cost-effective alternative in the base-case analysis (Table 4).

Regarding the results of a cost-effectiveness analysis using the RCT results as clinical outcomes, the lifetime cost for patients staying in the controlled state in the tiotropium group was estimated to be $9,943, about $1,650 more than the ICS/LABA group (Table 4). However, the cost of treating asthma exacerbations was estimated at $146 lower in the tiotropium group than in the ICS/LABA group. The expected total cost per patient over their lifetime was $1,504, which is costlier for the tiotropium group. The expected value for QALY was 0.018 greater than the ICS/LABA group. Thus, the ICER was calculated as $82,051/QALY.

In the subgroup analysis for frequent SABA users, there was a gain of 0.099 QALY in the tiotropium group compared to the ICS/LABA group. The lifetime cost for patients staying in the controlled state in the tiotropium group was estimated to be $1,703 more than the ICS/LABA group. However, the cost of treating asthma exacerbations in the tiotropium group was approximately $1,299 lower than the ICS/LABA group, which partially offset the cost of additional expenses caused by adding tiotropium. Thus, the ICER was calculated as $4,078/QALY. Subgroup analysis for frequent exacerbators showed similar trends. There was a QALY gain of 0.061 in the tiotropium group compared to the ICS/LABA group. The lifetime cost for patients in the controlled state in the tiotropium group was $1,293 higher than the ICS/LABA group, and treatment costs for asthma exacerbations in the tiotropium group were $784 lower than the ICS/LABA group, resulting in the

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ICER calculated at $8,332/QALY. These results show that the additional use of tiotropium was a cost-effective alternative for both subgroups.

The results of the sensitivity analysis by applying 0%, 3.5%, and 7% for the discount rate showed a change rate of 2.6% ($61,619/QALY), 0.7% ($60,488/QALY), and -0.8% ($59,582/QALY), respectively, from the base-case analysis in the ICER (Figure 2). In the scenario of change in the time horizon from a lifetime to three, five, and ten years, the ICER decreased by 8.0% ($55,258/QALY), 6.9% ($55,912/QALY), and 4.1% ($57,624/QALY), respectively. For the utility of asthma exacerbation, the scenario with the upper and lower limit with a 95% confidence showed that the ICER changed by 13.2% ($68,000/QALY) and -10.4% ($53,804/QALY), respectively, from the base-case analysis. Changing the mortality rate due to hospitalization as 1.5-fold of the original value showed that the ICER increased by 7.8% ($64,767/QALY) from the base-case analysis. In the scenario of a 10% increase or decrease in the cost of the controlled state, a change of 7.2% ($64,388/QALY and $55,760/QALY) was identified from the ICER of the base-case analysis. The same scenario for the cost of exacerbation state showed that the ICER altered by 2.8% ($61,768/QALY and $58,381/QALY) from the base-case analysis.

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Discussion

This study compared the effectiveness and costs of adding tiotropium to ICS/LABA for elderly patients with severe asthma in two phases. In phase I, we observed medical expenses and exacerbation from a retrospective cohort study based on RWD. Using the outcomes obtained in phase I, we estimated long-term costs and effectiveness with a Markov model through phase II. This approach, based on RWD, represents clinical practice, including data on asthma exacerbation and expenses. Furthermore, it has advantages in focusing on the elderly who are rarely eligible to participate in RCT and obtain outcomes across the severity of asthma. Although tiotropium was not cost-effective for all elderly patients, it was explicitly cost-effective for elderly patients with poorly controlled symptoms.

In phase I, the incidence rate of asthma exacerbation in the tiotropium group was 28% lower than that in the ICS/LABA group. This trend was constant in the subgroup analyses, and especially for frequent SABA users, more significant differences were evident. Our results using RWD of utilizing tiotropium for the elderly were consistent with previous studies targeting general adults. Two RCTs performed in severe asthma patients whose symptoms were not well-controlled despite using ICS/LABA showed that tiotropium decreased the risk of asthma exacerbation compared to ICS/LABA (RR: 0.71, 95 % CI: 0.55–0.92; RR: 0.80, 95 % CI: 0.61–1.04).[9] One pragmatic RCT study compared the risk of exacerbations before and after use showed a risk decrease of 27% due to tiotropium, similar to the results of this study.[27]

The ICER of cost-effectiveness analysis in the base case was $60,074/QALY, meaning that the addition of tiotropium was considered a non-cost-effective alternative. However, in previous RCT-based cost-effectiveness analyses performed in the United Kingdom and the United States, the addition of tiotropium was considered a cost-effective option within each healthcare system with ICER of £28,383/QALY and $34,478/QALY, respectively.[23, 28]

Three reasons explain the discrepancy between the ICER values in this study and those in previous studies. First, the healthcare systems in Korea and foreign countries are different, leading to varying medical expenses. Second, the target population of the current study is elderly patients, unlike existing

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studies, which targeted general adults. Third, the higher incidence rate of hospitalization due to exacerbation in the tiotropium group than in the ICS/LABA group.

The frequent hospitalization in the tiotropium group could be ascribed to the inherent bias in the cohort selection due to the methodological limitation of this study. Unlike RCTs based on random allocation, retrospective cohort design inevitably generates selection bias. In this study, the use of tiotropium may be evidence that the patient's disease is more severe and may increase asthma exacerbation frequency. Although we performed PS matching for potential confounding factors for asthma exacerbations to overcome this selection bias, there may exist residual confounding factors that could not be captured. Thus, it is possible that patients with a worse prognosis were assigned to the tiotropium group.

Despite the conservative study design disadvantageous to the tiotropium group, the results of subgroup analyses that targeted patients with more severe and uncontrolled symptoms showed that the addition of tiotropium is a cost-effective alternative. Since tiotropium is functionally selective for M3 receptors and has a longer and more robust anti-muscarinic action, patients whose symptoms could not be controlled with conventional asthma treatment alone may have shown greater effectiveness.[29, 30] In the subgroup analyses, the addition of tiotropium reduced the exacerbation treatment cost, partially offsetting the additional drug acquisition cost for tiotropium.

The calculated ICER from the analysis using the RCT, which confirmed the additional effect of tiotropium for general adults, was $82,051/QALY, showing that adding tiotropium is a non-cost-effectiveness alternative congruent with the base-case analysis. As the elderly population increases, so does their medical expenses. Policymakers need detailed standards to allocate limited healthcare resources for elderly patients with asthma efficiently. By using RWD, this study not only analyzed the elderly-specific cost-effectiveness profile for tiotropium, but also identified groups that would benefit most from using tiotropium among heterogeneous asthma patients by performing subgroup analysis according to the level of symptom control. Hence, research using RWD can provide a complementary basis when making policy judgments regarding targets that are intractable for RCTs.

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Our study has three main limitations. First, we used claims data based on reimbursements desired for healthcare costs and not for data with clinical purposes per se. Diagnostic coding was possibly incomplete, but previous studies that compared the diagnostic coding of claims data of Korea with actual medical records found the validity of diagnostic coding acceptable.[31, 32] Additionally, we confirmed our retrospective analysis design with healthcare professionals. Second, due to the nature of observational studies using claims data, there may exist residual confounding factors that could not be captured, such as smoking status, family history of asthma, food allergies, and living conditions of patients. Nevertheless, the uncertainty of an unmeasured confounder might be randomized and balanced among groups. Finally, we did not consider using biologic drugs recommended for severe asthma in the GINA guidelines because they were not yet reimbursed. The use of such biologic medicines was not noted in the claims data during our study periods. However, a clinical expert advised that few patients utilized them because of their high cost. Hence, biologic drugs were understood to affect the results of this study minimally.

Conclusion

The addition of tiotropium shows a higher cost-effectiveness profile when applied to elderly patients with severe asthma whose symptoms are poorly controlled: patients who were prescribed SABA four times or more in the past year, and patients who experienced asthma exacerbation more than once in the past year. By using RWE, our results provide information on the treatment effect of tiotropium beyond the clinical outcomes reported by RCTs and provide a complementary basis for establishing reimbursement criteria for tiotropium in elderly patients with severe asthma.

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None to declare.

Conflicts of interest

The authors declare that they have no relevant conflicts of interest.

Transparency declaration

None to declare.

Online repository

The online repository includes Tables E1, E2, E3, E4, E5, E6, E7, and Figure E1 and patient inclusion/exclusion criteria.

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Figure legends

FIGURE 1. Study overview, showing phases I and II.

FIGURE 2. Univariate sensitivity analysis results following the variation of key model inputs, presented in USD.

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Table 1. Model input parameters (base-case)

Model input	Value	Sources
Patient characteristics[a]		
% of Male	35.4	HIRA data
Age at the start, years	74.0	HIRA data
Transition probabilities		
Exacerbation rate in the tiotropium group, per cycle[b]		
SCS burst	0.0407	HIRA data
ED visit	0.0006	HIRA data
Hospitalization	0.0115	HIRA data
Exacerbation rate in the ICS/LABA group, per cycle[b]		
SCS burst	0.0631	HIRA data
ED visit	0.0007	HIRA data
Hospitalization	0.0086	HIRA data
Asthma-related mortality		
SCS burst	-	Assumption
ED visit	0.0021	Lee et al., 2018
Hospitalization	0.0021	Lee et al., 2018
All-cause mortality, per cycle[c]	Depending on age	Life table of Korea, 2017
Utilities		
Controlled state		
Tiotropium group	0.753	Wilson et al, 2014
ICS/LABA group	0.752	Wilson et al, 2014
Exacerbations		
SCS burst	0.57 (0.0109)[d]	Lloyd et al, 2007
ED visit	0.45[e] (0.0109)[d]	Assumption
Hospitalization[d]	0.33 (0.0109)[d]	Lloyd et al, 2007
Costs (USD[f])		
Controlled state, per cycle		
Tiotropium group	41	HIRA data
ICS/LABA group	34	HIRA data
Exacerbations, per event		
SCS burst	58	HIRA data
ED visit	98	HIRA data
Hospitalization	1,855	HIRA data

ED, emergency department; SCS, systemic corticosteroid.
[a]Average value for all PS-matched patients in both groups obtained from phase I study.
[b]Obtained from phase Ⅰ study.
[c]Values for all ages can be found in Table E6.
[d]Standard error, according to a previous study (Willson, 2004). This value was utilized in the sensitivity analysis.
[e] Average value between 0.57 and 0.33.
[f]1 USD = 1,101.08 KRW.

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Table 2. Baseline characteristics of patients in the retrospective cohort study

	Entire cohort			PS matched cohort		
	Tiotropium + ICS/LABA (N = 286)	ICS/LABA (N = 4,452)	SMD	Tiotropium + ICS/LABA (N = 274)	ICS/LABA (N = 822)	SMD
Male, %	36.4	28.9	**0.160**	35.8	36.0	-0.005
Age, mean (SD)	74.6 (6.4)	74.0 (6.2)	**0.104**	74.5 (6.37)	74.6 (6.53)	-0.012
Type of insurance, %						
Health insurance	86.0	85.1	0.026	86.1	83.8	**0.065**
Medical aid	14.0	14.9		13.9	16.2	
Level of the medical institution at the index date, %						
Hospital	92.3	45.9	**-1.160**	92.0	91.4	-0.022
Clinics or public health center	7.7	54.1		8.0	8.6	
CCI score, mean (SD)	3.53 (2.15)	2.94 (1.85)	**0.291**	3.44 (2.09)	3.51 (2.16)	-0.030
Pre-index comorbidity, %						
Hypertension (Uncomplicated)	60.8	57.9	0.059	59.9	61.2	-0.027
Hypertension (Complicated)	12.2	9.3	0.096	12.4	10.6	0.057
Hyperlipidemia	55.9	50.1	**0.118**	54.7	55.5	-0.015
GERD	65.4	57.7	**0.159**	65.0	61.8	0.066
Arrhythmia	4.6	3.2	0.069	4.4	3.5	0.044
Depression	19.2	14.7	**0.122**	19.3	14.7	0.123
Anxiety	20.3	25.1	**-0.115**	21.2	22.4	**-0.024**
Atopy	3.2	5.4	**-0.113**	2.9	4.7	**-0.095**
Rhinitis	85.3	85.9	-0.018	85.8	87.2	-0.043
Sinusitis	28.3	28.1	0.005	28.5	27.3	0.027
Diabetes (Uncomplicated)	18.9	17.0	0.049	18.3	18.3	0.000
Diabetes (Complicated)	24.8	15.0	**0.248**	24.8	20.9	0.093
Congestive heart failure	15.7	8.7	**0.215**	14.2	15.8	-0.044
Dementia	6.3	7.0	-0.029	6.6	5.7	0.035
Ischemic heart diseases	23.1	18.3	**0.117**	22.6	21.8	0.020
Other heart diseases	18.2	10.7	**0.214**	17.5	14.8	**0.073**
Cerebrovascular diseases	15.4	15.2	0.006	15.7	15.0	0.020
Renal failure	4.9	2.5	**0.130**	3.3	4.5	-0.063
COPD	21.0	10.5	**0.292**	20.1	20.3	**-0.006**
Main pulmonary diseases	71.7	58.7	**0.275**	71.2	71.4	-0.005
Other pulmonary diseases	90.2	84.1	**0.182**	89.8	89.8	0.000
Asthma-related healthcare resources utilization in the pre-index period						
Outpatient visits, mean (SD)	12.5 (10.2)	11.2 (10.2)	**0.130**	11.8 (9.35)	11.3 (10.8)	0.048
ED visits, mean (SD)	0.06 (0.25)	0.08 (0.81)	-0.027	0.05 (0.23)	0.05 (0.34)	0.008
Hospitalizations, mean (SD)	0.74 (0.97)	0.40 (0.81)	**0.384**	0.72 (0.95)	0.68 (1.05)	0.032
SABAs use, mean (SD)	3.89 (5.81)	2.61 (5.79)	**0.221**	3.42 (4.64)	3.36 (6.34)	0.011
4 ≤ SABAs use, %	31.5	20.1	**0.263**	29.9	26.6	0.073
Histories of asthma exacerbation in the pre-index period						
1 Exacerbation, %	42.0	44.9	-0.060	43.4	43.7	-0.005
2 Exacerbations, %	19.6	20.1	-0.014	19.7	21.7	-0.048
3 Exacerbations, %	11.5	10.5	0.034	12.0	11.7	0.011
4 ≤ Exacerbations, %	26.9	24.5	0.056	24.8	23.0	0.043
SCS burst, mean (SD)	3.56 (8.56)	2.92 (4.90)	0.092	2.82 (6.42)	2.89 (5.32)	-0.011
ED visit, mean (SD)	0.03 (0.17)	0.05 (0.36)	-0.076	0.03 (0.17)	0.02 (0.15)	0.077
Hospitalization, mean (SD)	0.51 (0.77)	0.27 (0.59)	**0.343**	0.49 (0.75)	0.48 (0.73)	0.011

CCI, Charlson comorbidity index; *ED*, emergency department; *ICS*, inhaled corticosteroid; *PS*, propensity score; *SABA*, short-acting beta-agonist; *SMD*, standardized mean difference.

Bold indicates standardized mean differences ≥ 0.1.

†Tested by Fisher's exact test.

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Table 3. Annual incidence rate of asthma exacerbations and rate ratio

Patient group	Number of exacerbations, Mean (SD)				RR
	SCS burst	ED visit	Hospitalization	Total	(95% CI)
Total					
Tiotropium + ICS/LABA (N=274)	1.24 (4.28)	0.01 (0.12)	0.30 (0.76)	1.55 (4.33)	0.72 (0.62–0.83)
ICS/LABA (N=822)	1.84 (4.52)	0.02 (0.13)	0.23 (0.66)	2.09 (4.67)	
Subgroup: frequent SABA user[a]					
Tiotropium + ICS/LABA (N=65)	2.40 (7.51)	0.03 (0.17)	0.34 (0.99)	2.77 (7.51)	0.68 (0.60–0.85)
ICS/LABA (N=195)	3.47 (7.32)	0.03 (0.16)	0.37 (0.80)	3.87 (7.55)	
Subgroup: frequent exacerbator[b]					
Tiotropium + ICS/LABA (N=148)	2.11 (5.84)	0.01 (0.12)	0.30 (0.71)	2.43 (5.86)	0.77 (0.65–0.88)
ICS/LABA (N=444)	2.67 (5.69)	0.02 (0.15)	0.31 (0.74)	2.99 (5.83)	

ED, emergency department; *SABA*, short-acting beta-agonist; *RR*, rate ratio*; SCS*, systemic corticosteroid.
The rate ratio was calculated using Poisson regression and adjusted for pre-index period comorbidities (dementia, diabetes with complications, and frequent use of SABA).
[a]Patients who were prescribed SABA four times or more in the past year.
[b]Patients who experienced asthma exacerbation more than once in the past year.

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Table 4. Cost-effectiveness analysis results

Outcomes	The modeled frequency of clinically significant exacerbations			Effectiveness	Cost (USD)			Cost-Effectiveness
	SCS burst	ED visit	Hospitalization	QALYs	Controlled state	Treatment for exacerbation	Total costs	ICER (USD/QALY)
Base case								
Tiotropium + ICS/LABA	11.31	0.09	2.70	6.90	9,907	5,673	15,580	**60,074**
ICS/LABA	17.13	0.19	2.16	6.87	8,269	5,030	13,299	
Incremental				**0.038**			**2,281**	
RCT as clinical outcomes								
Tiotropium + ICS/LABA	4.31	0	0.45	7.02	9,943	1,081	11,024	**82,051**
ICS/LABA	5.42	0	0.49	7.00	8,293	1,227	9,520	
Incremental				**0.018**			**1,504**	
Subgroup analysis: frequent SABA user[a]								
Tiotropium + ICS/LABA	21.24	0.27	3.01	6.82	10,760	6,114	16,875	**4,078**
ICS/LABA	32.28	0.28	3.44	6.72	9,057	7,413	16,471	
Incremental				**0.099**			**404**	
Subgroup analysis: frequent exacerbator[b]								
Tiotropium + ICS/LABA	18.69	0.09	2.66	6.85	9,534	6,028	15,563	**8,332**
ICS/LABA	24.86	0.19	2.89	6.79	8,241	6,812	15,053	
Incremental				**0.061**			**509**	

RCT, randomized controlled trial; SABA, short-acting beta-agonist; SCS, systemic corticosteroid; ED, emergency department; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.
[a]Patients who were prescribed SABA four times or more in the past year.
[b]Patients who experienced asthma exacerbation more than once in the past year.

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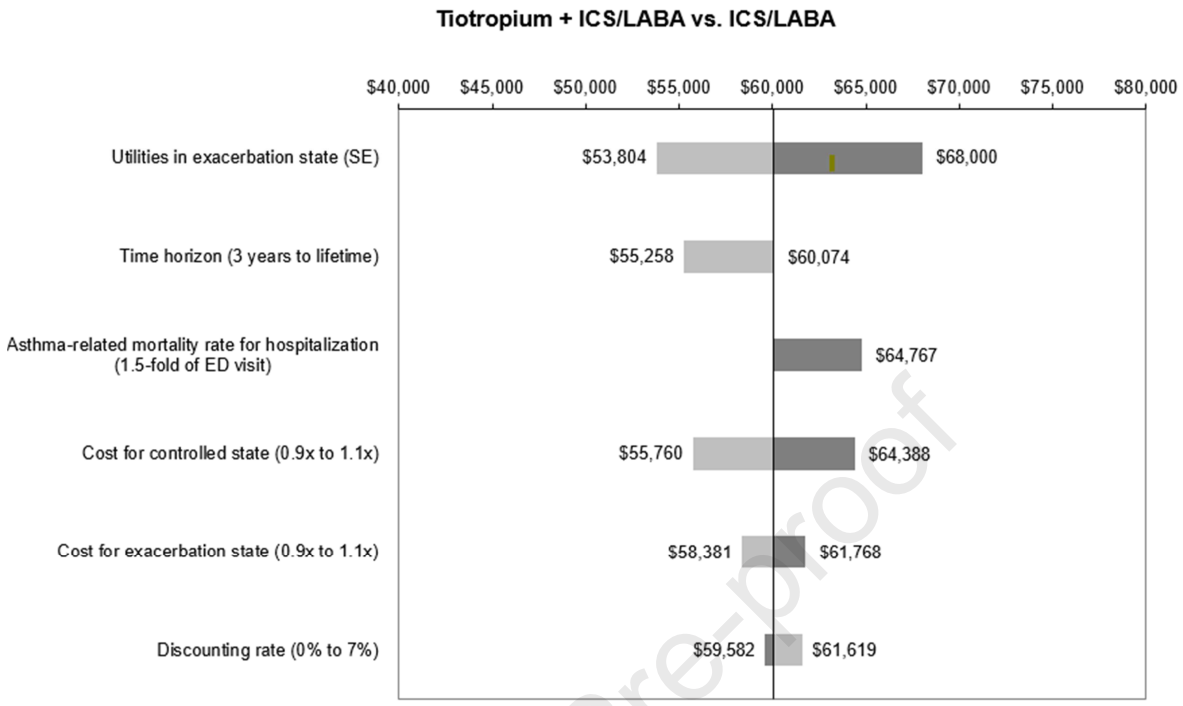

FIGURE 2.

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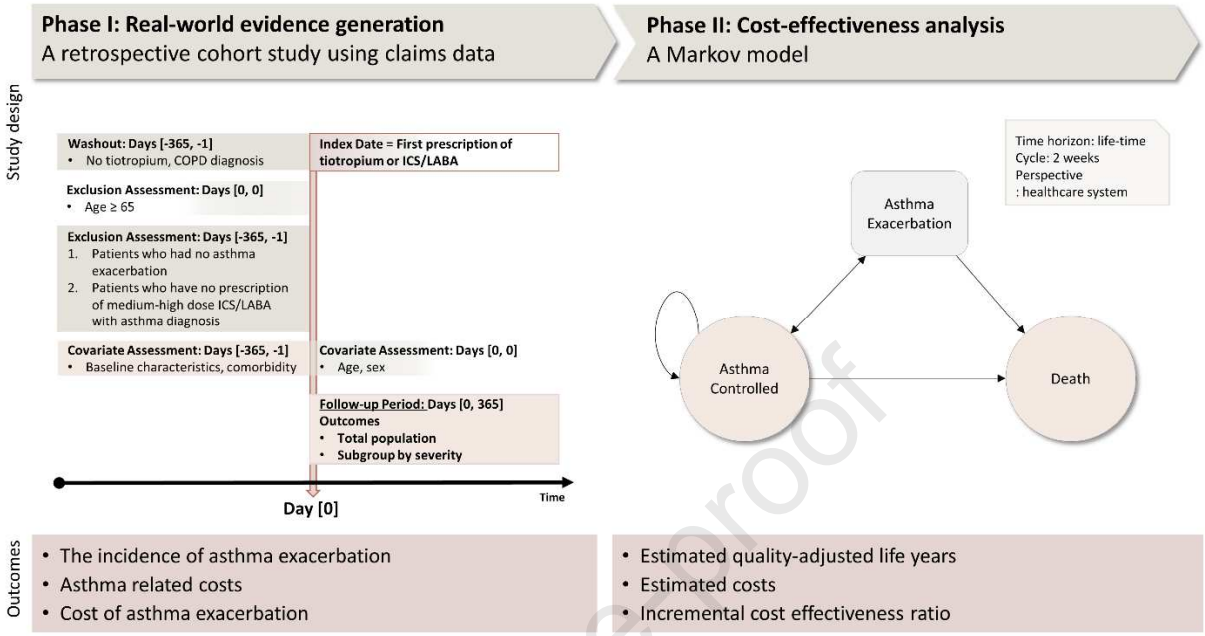

FIGURE 1.

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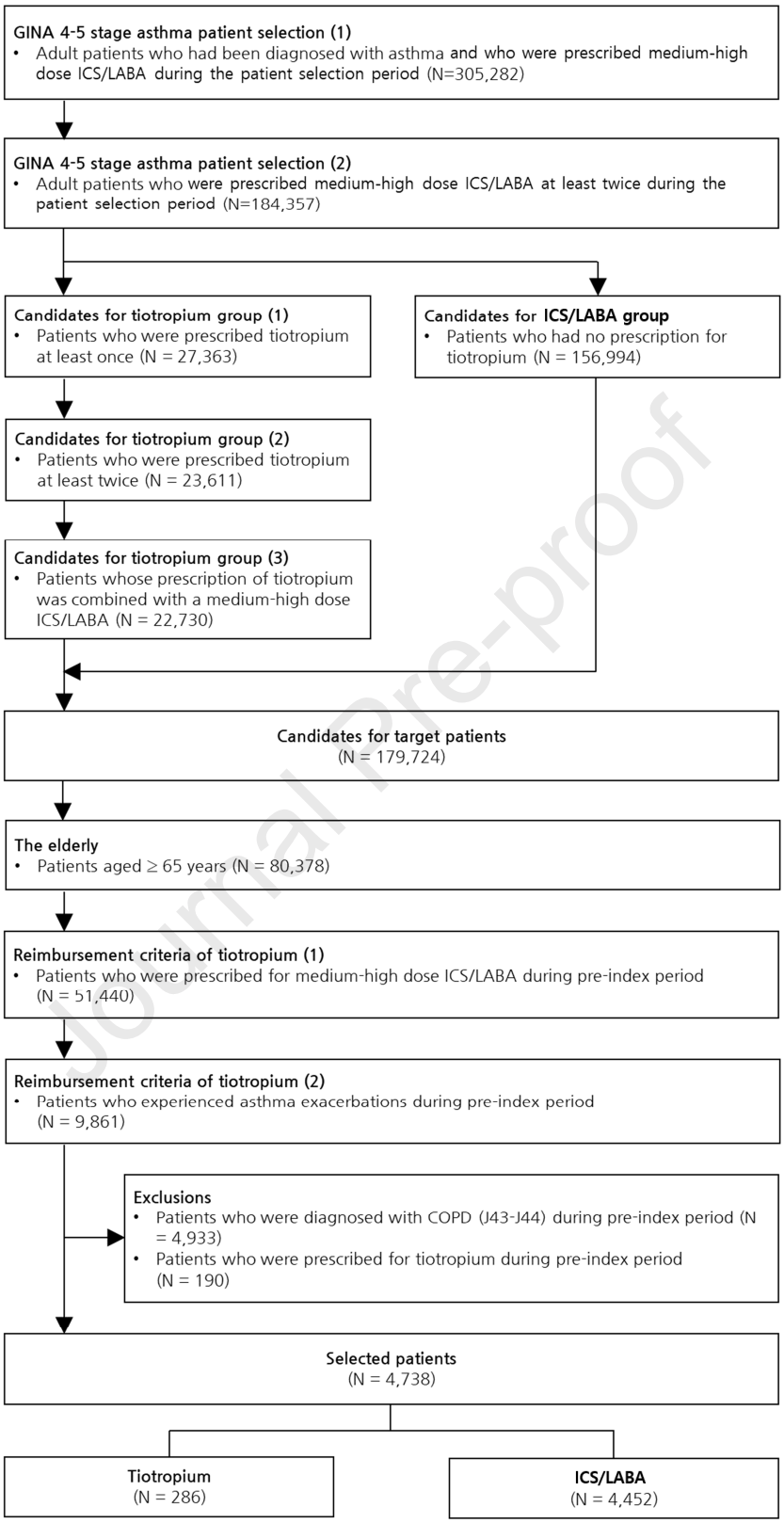
GINA 4-5 stage asthma patient selection (1)
• Adult patients who had been diagnosed with asthma and who were prescribed medium-high dose ICS/LABA during the patient selection period (N=305,282)
GINA 4-5 stage asthma patient selection (2)
• Adult patients who were prescribed medium-high dose ICS/LABA at least twice during the patient selection period (N=184,357)
Candidates for tiotropium group (1)
• Patients who were prescribed tiotropium at least once (N = 27,363)
Candidates for ICS/LABA group
• Patients who had no prescription for tiotropium (N = 156,994)
Candidates for tiotropium group (2)
• Patients who were prescribed tiotropium at least twice (N = 23,611)
Candidates for tiotropium group (3)
• Patients whose prescription of tiotropium was combined with a medium-high dose ICS/LABA (N = 22,730)
Candidates for target patients
(N = 179,724)
The elderly
• Patients aged ≥ 65 years (N = 80,378)
Reimbursement criteria of tiotropium (1)
• Patients who were prescribed for medium-high dose ICS/LABA during pre-index period (N = 51,440)
Reimbursement criteria of tiotropium (2)
• Patients who experienced asthma exacerbations during pre-index period (N = 9,861)
Exclusions
• Patients who were diagnosed with COPD (J43-J44) during pre-index period (N = 4,933)
• Patients who were prescribed for tiotropium during pre-index period (N = 190)
Selected patients
(N = 4,738)
Tiotropium
(N = 286)
ICS/LABA
(N = 4,452)

Figure E1.