약학 석사학위 논문

안지오텐신 전환 효소 억제제 개시 이후 진해제의 사용 분석

Use of Antitussives After the Initiation of Angiotensin-Converting Enzyme Inhibitors

2017년 8월

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지도교수 홍 송 희

이 논문을 권익태 석사학위논문으로 제출함

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권익태의 석사학위논문을 인준함

2017년 6월

위 원 장 _____ (인)

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Abstract

Use of Antitussives After the Initiation of Angiotensin-Converting Enzyme Inhibitors

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Background

Angiotensin-converting enzyme inhibitors (ACEI) can induce a dry cough, more frequently among Asians. If healthcare professionals fail to detect coughs induced by an ACEI, patients are at risk of getting antitussives inappropriately instead of discontinuing ACEI. The purpose of this study was to examine how the initiation of ACEI affects the likelihood of antitussive uses compared with the initiation of Angiotensin Receptor Blocker (ARB) and to determine the effect of the antitussive use on the duration and adherence of therapy in a Korean population.

Method

This study is a retrospective analysis of the Korean National Health Insurance Service (KNHIS) National Sample Cohort (NSC) 2002-2013. Adult patients who were initiated with ACEI or ARB in 2004-2012 were selected. The ACEI group and the ARB group were

matched by the propensity score. The covariates that can affect the likelihood of antitussive treatment were identified using the Andersen's behavioral model of health services utilization. A multivariate logistic regression was used to assess the likelihood of antitussive use after the initiation of ACEI and the likelihood of hospital switching. The difference in duration of ACEI therapy was tested using a t-test. The difference in ACEI therapy adherence, which was measured by prescription days covered, were tested using the chi-squared test.

Results

A total 19,793 patients who were initiated with ACEI in 2004-2012 were matched with 39,586 patients who were initiated with ARB in in the same period. The initiation of ACEI was significantly associated with the likelihood of antitussive treatment (OR 2.241; 95% CI 2.142-2.345). In terms of the type of hospitals where the ACEI was initiated, the likelihood of the hospital switch is significantly lower for primary than tertiary hospitals (OR 0.069; 95% CI 0.057-0.083). However in terms of hype of hospitals where the antitussives were first prescribed after the ACEI initiation, the primary hospitals were significantly more associated with the hospital switching than tertiary hospitals (OR 26.806; 95% CI 21.173-33.937) The patients who were treated with antitussives after the ACEI initiation were on ACEI therapy longer than those who did not use antitussives (mean ± SD 117.9 ± 80.4 days vs. 112.0 ± 84.6 days; $p < 0.001$). The long-term ACEI therapy adherence was lower in patients with antitussive use than those without antitussive use (46.1% vs. 49.5%, $p = 0.012$).

Conclusion

This study found that the cough patients who were initiated with ACEI are often treated symptomatically with antitussives in Korea, instead of discontinuing ACEI. The antitussive treatment decreased the ACEI therapy adherence. A preventive approach from inappropriate prescription of antitussives secondary to ACEI-induced cough would be necessary.

Key words : Angiotensin-Converting Enzyme Inhibitor, Cough, Antitussive

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I. Introduction

Angiotensin-Converting Enzyme Inhibitor (ACEI) is used as a primary drug in many chronic diseases, especially in hypertension, heart failure, and chronic kidney disease, by inhibiting the Renin-Angiotensin-Aldosterone System (RAAS) (Brugts et al., 2009). The incidence of ACEI-induced adverse drug reactions was reported to be lower than that of other cardiovascular drugs, but the most common side effect of ACEI is a dry cough, which is known to be the major cause of poor tolerability (Israili & Hall, 1992). The incidence of ACEI-induced cough is about 5-20% among Western populations, but is two times higher among Asians (Woo KS & Nicholls, 1995; Na et al., 2000; Ng & Goh, 2014). It was reported that ACEI-induced cough usually occurs within 4 weeks after the drug initiation although it may be delayed up to 6 months (Israili et al., 1992). The symptom resolves within several weeks after the discontinuation of the drug (Israili et al., 1992). Therefore, instead of using antitussives for the cough, most medical guidelines that were revised in the early 2000s, including the JNC-7 hypertension guidelines, 2005 ACCF/AHA heart failure guidelines, and 2004 KDOQI chronic kidney disease guidelines recommended to switch to Angiotensin II Receptor Blocker (ARB) which has similar mechanism of action with a much lower rate of cough compared to ACEI (Chobanian et al., 2003; Hunt et al., 2005; Kidney Disease Outcomes Quality Initiative, 2004).

In Korea, a previous study reported that the incidence of ACEI-induced cough in Koreans is 40.1% with a significant risk factor of female gender (Na et al., 2000). Since the primary care physician system is not present in Korea, patients in Korea often switch their physician (Shin et al., 2011); for example, if a patient

with newly prescribed ACEI visits a physician other than the original ACEI prescriber such as otolaryngologist due to a cough, the physician will find it difficult to determine whether the patient is suffering from a simple acute upper respiratory infection such as a common cold or a side effect caused by ACEI. Therefore it is expected that the rate of cough misdiagnosis and inappropriate antitussive prescription of domestic ACEI patients in Korea is expected to be high.

The aims and hypotheses of this study are following:

Aim 1: initiation of ACEI increases the antitussive use.
Hypothesis 1: the likelihood of antitussive use after the ACEI or ARB initiation is higher for patients who were initiated with ACEI than those who were initiated with ARB.

Aim 2: hospital switching is more common in primary hospitals.
Hypothesis 2: the likelihood that the hospital of ACEI initiation and the hospital of antitussive prescription after ACEI initiation are different is higher for primary hospitals than tertiary hospitals.

Aim 3: ACEI therapy is discontinued if ACEI-induced cough is appropriately managed.
Hypothesis 3: the duration of ACEI therapy is longer in patients who were treated with antitussives after ACEI initiation than those who were did not use antitussives after ACEI initiation.

Aim 4: antitussive use in ACEI-induced cough will reduce the ACEI adherence.
Hypothesis 4: the ACEI adherence is lower in patients who were treated with antitussives after ACEI initiation than those who did not use antitussives after ACEI initiation.

II. Literature Review

1. ACEI-induced Cough

The first ACEI, captopril was approved by FDA in 1981, and since then the risk of cough was widely reported (Chung & Pavord, 2008). There were a few attempts to manage ACEI-induced cough with nonsteroidal antiinflammatory drugs and aspirin, but those drugs were not studied in large scales (Gilchrist, Richards, March, & Nicholls, 1989; Fogari et al., 1992; Dicpinigaitis, 1996; Tenenbaum et al., 2000; Dykewicz, 2004). Therefore the golden rule of ACEI-induced cough treatment has been to discontinue the ACEI (Kim et al., 2014), and since the ARB came into the market, the market share of ACEI has been decreased (Bian, Kelton, Guo, & Wigle, 2010). However, Cáceres et al. (2015) reported that although the share of ARB increased over ACEI in Spain since 2007, ACEI is still the second most frequently prescribed antihypertensive drug class in 2012, and enalapril was the most frequently prescribed antihypertensive ingredient. Xu et al. (2015) also reported that ACEI accounts for 13.3% of antihypertensive prescription in China in 2012. In the United States, a national survey by Gu et al. (2012) revealed that ACEI was the second most frequently prescribed drug class overall, and was most frequently used as a monotherapy in 2009-2010. Thus, ACEI is still a popular antihypertensive drug class today, and healthcare professional must be aware of the ACEI-induced adverse effects and how to manage them.

Although the incidence of ACEI-induced cough is well studied, there are only a few studies were conducted to assess the antitussive use on ACEI-induced cough. A survey by Lombardi et

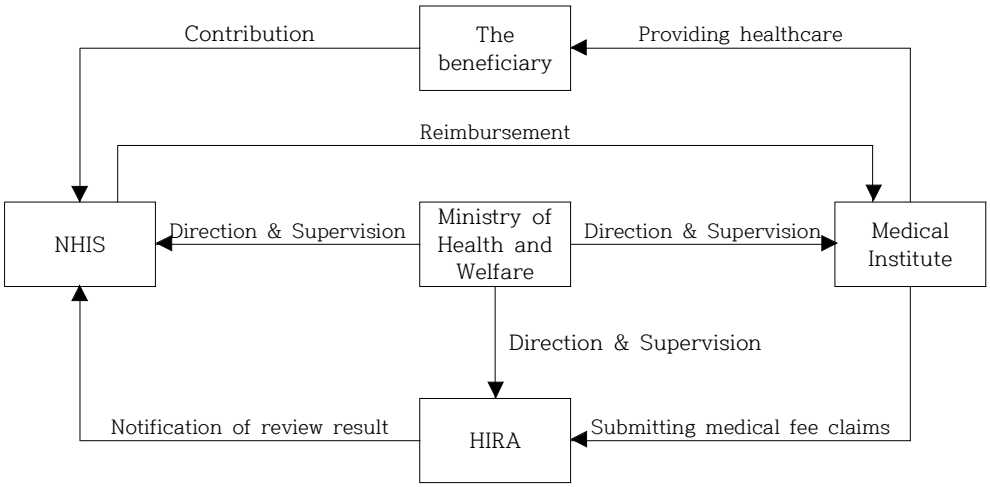
al. in 2005 showed that among 154 physicians, 92.9% answered to treat ACEI-induced cough symptomatically (Lombardi et al., 2005). Vegter et al. (2010) reported that 15% of patients in Netherlands with newly prescribed ACEI were mistreated with antitussives, and Vegter et al. (2013) also revealed that the ACEI therapy adherence of the patients with antitussive mistreatment was 52.4%, significantly lower than ACEI patients without antitussives (75.2%). However, they used InterAction Database of the Netherlands (IADB.nl), which collects prescription records of only 500,000 subjects.

2. Korean National Health Insurance Service National Sample Cohort

This study used the Korean National Health Insurance Service (KNHIS) National Sample Cohort (NSC) 2002-2013. South Korea has provided universal healthcare coverage since 1989 (Kwon, 2009), and enrolling at the KNHIS is mandatory to all civilians. In 2015, 97.0% of the total population was enrolled to the KNHIS, and 3.0% was covered by the medical aid programs (Ryu, 2017). When the health insurance beneficiaries use medical institutions, the Health Insurance Review & Assessment Service (HIRA) reviews the fees charged by the medical institutions. Then the results are sent to the KNHIS, and KNHIS will pay the amount requested by the medical institutions (Figure 1) (Ryu, 2017). Therefore, all data related to the national healthcare utilization is stored in the HIRA and NHIS databases, and can be used for research purposes.

The NSC 2002-2013 which was released by KNHIS in 2015 includes 1,025,340 random subjects to represent entire Korean population of 46,605,433 in 2002. The KNHIS NSC maintained the

Figure 1. Structure of the National Health Insurance Program in Korea (Ryu, 2017)



HIRA = health insurance review and assessment service; NHIS = national health insurance service

sample of 2002 until 2010 and added the sample of newborn that occurred every year considering the natural decrease of the number of samples caused by data loss due to loss of qualification such as death or immigration. Thus the structure of NSC is a semi-dynamic cohort structure (Figure 2) (Lee et al., 2012). The database includes demographic information and all medical claims of the subjects. More detailed composition of the database is shown in Table 1.

Figure 2. Structure of the Korean National Health Insurance Service National Sample Cohort (Lee et al., 2012)

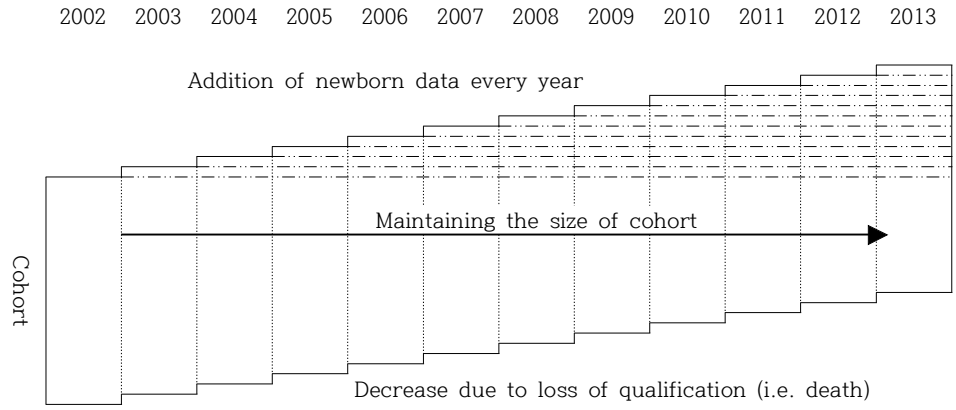


Table 1. Composition of the Korean National Health Insurance Service National Sample Cohort

Database	Details
Qualification DB	Demographic information: gender, age, area of residence, insurance type, income level, date and cause of death, etc.
Medical DB	Details on medical claims by the institutions
Medical Statement	Personal ID, statement key code, etc.
Medical History	Inpatient treatment records
Diagnosis	Detailed diagnosis records
Prescription	Outpatient prescription records
Health Examination DB	Main results of health screening and lifestyle and behavior related questionnaires. (Note: health examination data of medical aid beneficiaries is not included.)
Medical Institution DB	Hospital category, establishment category, regional status, facilities, equipments, human power, etc.

III. Method

1. Study Design and Subjects

This study is a retrospective analysis of the KNHIS NSC 2002-2013. Study subjects consisted of adults older than or equal to 20 years of age who were initiated with ACEI or ARB between January 2004 and December 2012. The age was based on the year when the ACEI or ARB was initiated on each subject. The initiation was defined that the either class of medications had not been prescribed for at least 365 days (Figure 3). ACEI was determined based on ATC codes C09A and C09B while ARB was defined as ATC codes C09C and C09D, and the drugs that were available in Korea were selected via Korea Pharmaceutical Information Service by HIRA (Table 2). Then the ACEI group and ARB group matched by 1:2 to age, sex, area of residence, income level, and insurance type based on the propensity score were generated (Figure 4).

Figure 3. Screening, Inclusion, and Follow up Periods

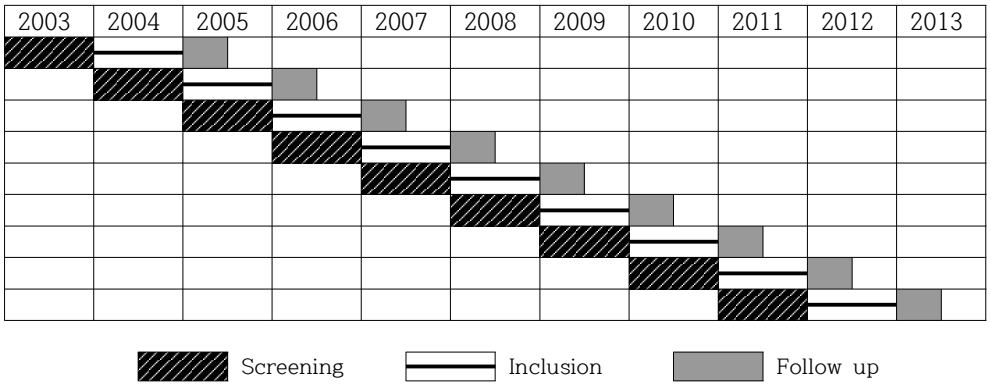
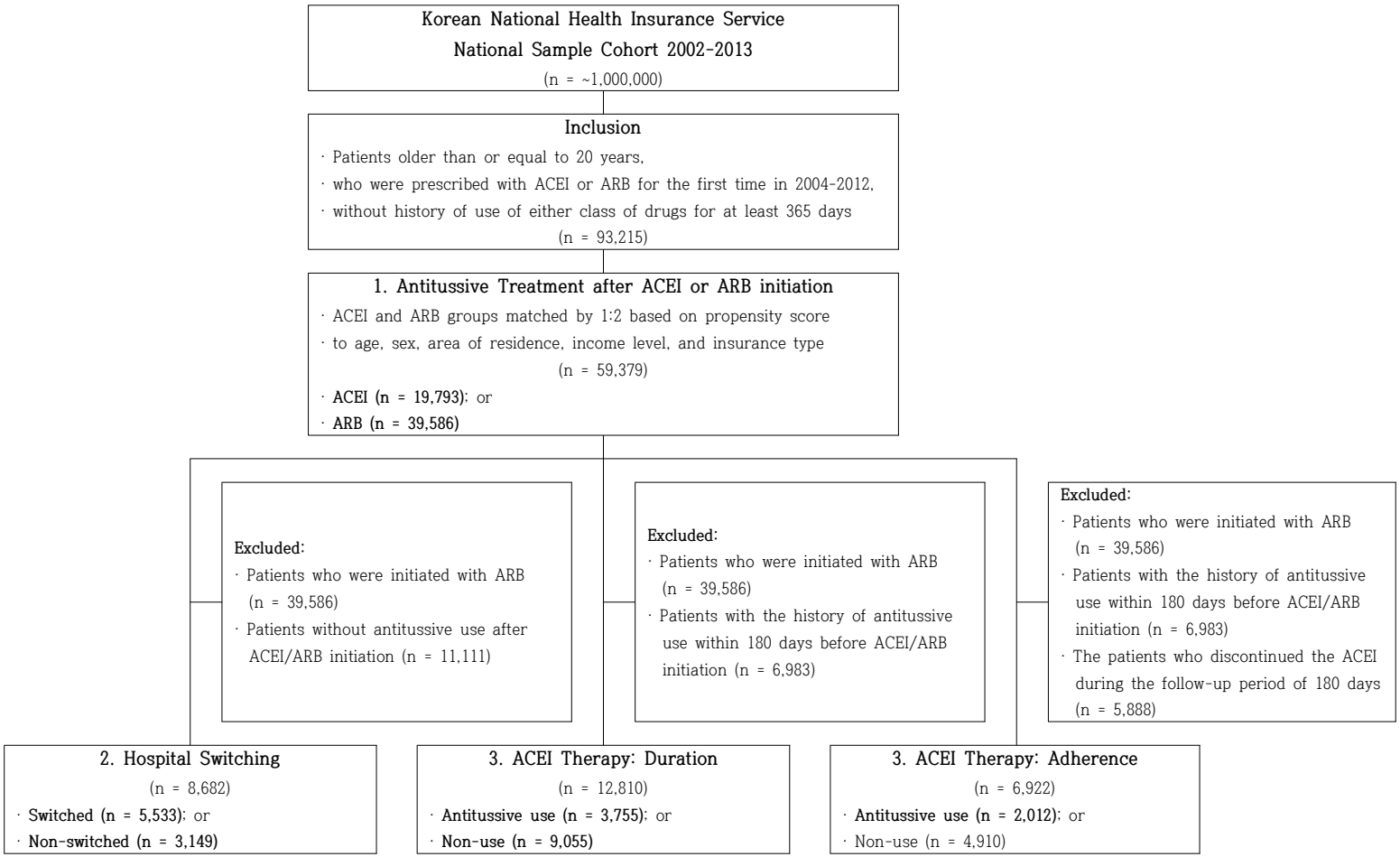


Table 2. ATC Codes and Generic Names of ACEI and ARB

ATC code	Generic Name	ATC code	Generic Name
C09 Agents acting on the renin-angiotensin system			
C09A ACE inhibitors, plain		**C09C Angiotensin II antagonists, plain**	
C09AA ACE inhibitors, plain		*C09CA Angiotensin II antagonists, plain*	
C09AA01	Captopril	C09CA01	Losartan
C09AA02	Enalapril	C09CA02	Eprosartan
C09AA03	Lisinopril	C09CA03	Valsartan
C09AA04	Perindopril	C09CA04	Irbesartan
C09AA05	Ramipril	C09CA06	Candesartan
C09AA06	Quinapril	C09CA07	Telmisartan
C09AA07	Benazepril	C09CA08	Olmesartan medoxomil
C09AA08	Cilazapril	C09CA10	Fimasartan
C09AA09	Fosinopril		
C09AA13	Moexipril		
C09AA14	Temocapril		
C09AA15	Zofenopril		
C09AA16	Imidapril		
C09B ACE inhibitors, combinations		**C09D Angiotensin II antagonists, combinations**	
C09BA ACE inhibitors and diuretics		*C09DA Angiotensin II antagonists and diuretics*	
C09BA01	Captopril and diuretics	C09DA01	Losartan and diuretics
C09BA02	Enalapril and diuretics	C09DA02	Eprosartan and diuretics
C09BA03	Lisinopril and diuretics	C09DA03	Valsartan and diuretics
C09BA04	Perindopril and diuretics	C09DA04	Irbesartan and diuretics
C09BA05	Ramipril and diuretics	C09DA06	Candesartan and diuretics
C09BA13	Moexipril and diuretics	C09DA07	Telmisartan and diuretics
		C09DA08	Olmesartan medoxomil and diuretics
C09BB ACE inhibitors and calcium channel blockers		*C09DB Angiotensin II antagonists and calcium channel blockers*	
C09BB05	Ramipril and felodipine	C09DB01	Valsartan and amlodipine
C09BB06	Enalapril and nitrendipine	C09DB02	Olmesartan medoxomil and amlodipine
		C09DB04	Telmisartan and amlodipine
		C09DB06	Losartan and amlodipine
		C09DB07	Candesartan and amlodipine
		C09DB08	Valsartan and lercanidipine
		C09DX Angiotensin II antagonists, other combinations	
		C09DX03	Olmesartan medoxomil, amlodipine and hydrochlorothiazide
		C09DX04	Valsartan and sacubitril

ATC = Anatomical Therapeutic Chemical; ACEI = Angiotensin-Converting Enzyme Inhibitor; ARB = Angiotensin II Receptor Blocker

Figure 4. Flowchart of the Study Subject Selection Process



2. Measurements

Antitussive treatment after ACEI or ARB initiation

Antitussive treatment was determined based on the antitussive use within 180 days after ACEI or ARB initiation (Figure 3), since ACEI induced cough may start up to 6 months after ACEI initiation, as the previous literature reported (Israili et al., 1992). Antitussives were defined as ATC codes R05C and R05D, and the drugs that were available in Korea were selected via Korea Pharmaceutical Information Service (Table 3).

Other variables that can affect the likelihood of antitussive treatment were identified using the Andersen's behavioral model of health services utilization (Figure 5) (Anderson, 1995). It is

Figure 5. Andersen's Behavioral Model and Utilized Variables

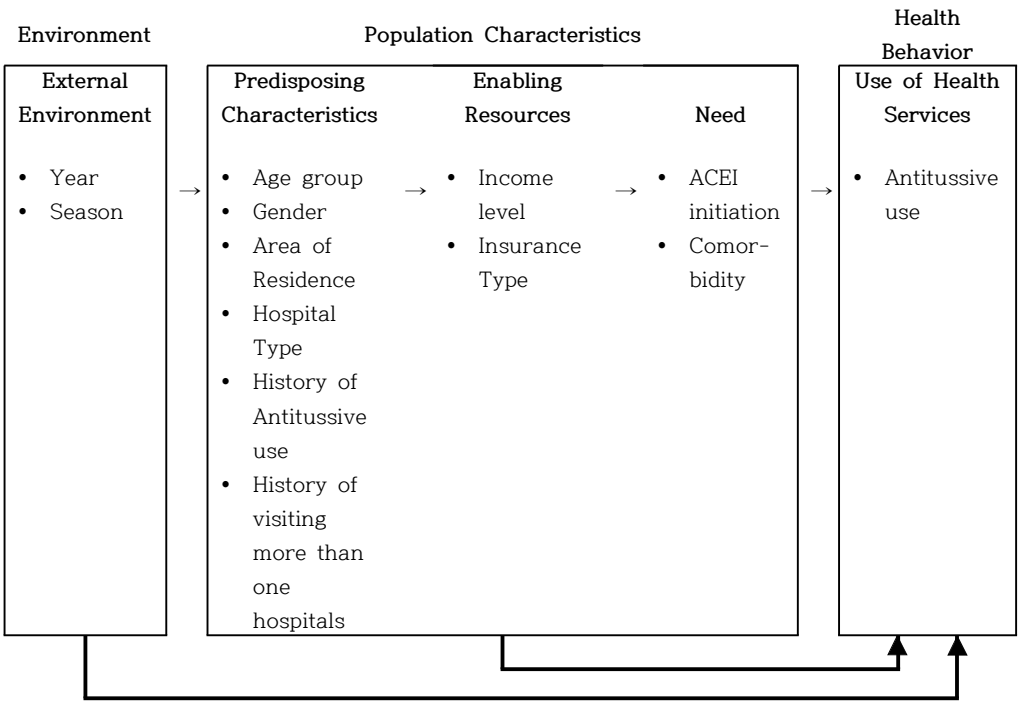


Table 3. ATC Codes and Generic Names of Antitussives

ATC code	Generic Name	ATC code	Generic Name
R05 Cough and cold preparations			
R05C Expectorants, excluding combinations with cough suppressants		R05D Cough suppressants, excluding combinations with expectorants	
R05CA Expectorants		*R05DA Opium alkaloids and derivatives*	
R05CA03	Guaifenesin	R05DA04	Codeine
R05CA10	Combinations	R05DA09	Dextromethorphan
R05CA12	Hederae helicis folium	R05DA20	Combinations
R05CB Mucolytics		*R05DB Other cough suppressants*	
R05CB01	Acetylcysteine	R05DB01	Benzonatate
R05CB02	Bromhexine	R05DB02	Benproperine
R05CB03	Carbocisteine	R05DB05	Pentoxyverine
R05CB06	Ambroxol	R05DB07	Oxolamine
R05CB07	Sobrerol	R05DB13	Butamirate
R05CB09	Letosteine	R05DB15	Zipeprol
R05CB10	Combinations	R05DB19	Dropropizine
R05CB14	Neltenexine	R05DB20	Combinations
R05CB15	Erdosteine	R05DB21	Cloperastine
		R05DB24	Tipepidine
		R05DB27	Levodropropizine
R05F Cough suppressants and expectorants, combinations			
R05FA Opium derivatives and expectorants			
R05FA01	Opium derivatives and mucolytics		
R05FA02	Opium derivatives and expectorants		
R05FB Other cough suppressants and expectorants			
R05FB01	Cough suppressants and mucolytics		
R05FB02	Cough suppressants and expectorants		

composed of external environment and population characteristics categories, and the population characteristics is composed of predisposing characteristics, enabling resources, and need. The external environment was composed of year and season (spring, summer, autumn or winter) of ACEI/ARB initiation. The seasons were determined by the meteorological definition: spring from

March to May, summer from June to August, autumn from September to November, and winter from December to February. The predisposing characteristics was consisted of age (<40, 40-49, 50-59, 60-69, 70-79, or ≥80 years), gender, area of residence (Seoul, metropolitan city, city, or rural area), type of hospital where ACEI/ARB was initiated, history of antitussive use within 180 days before ACEI/ARB initiation, and history visiting more than one hospitals. The enabling resource was composed of income level (≤20%, 20%-40%, 40%-60%, 60%-80%, >80% of the median) and the type of insurance (employee insured, self-employed insured, medical aid). The need was consisted of the initiation of ACEI, and comorbidity. Comorbidity was measured by Charlson comorbidity index (Charlson, Pompei, Ales, & MacKenzie, 1987) and was constructed by summing weights assigned to International Statistical Classification of Diseases (ICD) codes 10th Revision (ICD-10) reported from the data (Table 4) (Sundararajan et al., 2004).

Hospital switching

Hospital switching was defined that the identification code of hospital which prescribed antitussive after the ACEI initiation is different from the identification code of hospital which prescribed ACEI. The ARB group was excluded in this analysis, and patients who were not prescribed with antitussives after the ACEI initiation were also excluded. The variables that can affect the likelihood of hospital switching in this analysis was similar to ones that were utilized in the previous model, but type of hospital where antitussive was first prescribed after ACEI initiation was also considered in this analysis.

Table 4. Diagnostic categories of Charlson Comorbidity Index and Corresponding ICD-10 Codes (Sundararajan et al., 2004)

Condition	Weights	ICD-10 Codes
Acute myocardial infarction	1	I21, I22, I252
Congestive heart failure	1	I50
Peripheral vascular disease	1	I71, I790, I739, R02, Z958, Z959
Cerebral vascular accident	1	I60, I61, I62, I63, I65, I66,G450, G451, G452, G458, G459, G46, I64, G454, I670, I671, I672, I674, I675, I676, I677 I678, I679, I681, I682, I688, I69
Dementia	1	F00, F01, F02, F051
Pulmonary disease	1	J40, J41, J42, J44, J43, J45, J46, J47, J67, J44, J60, J61, J62, J63, J66, J64, J65
Connective tissue disorder	1	M32, M34, M332, M053, M058, M059, M060, M063, M069, M050, M052, M051, M353
Peptic ulcer	1	K25, K26, K27, K28
Liver disease	1	K702, K703, K73, K717, K740, K742, K746, K743, K744, K745
Diabetes	1	E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135, E145
Diabetes complications	2	E102, E112, E132, E142 E103, E113, E133, E143 E104, E114, E134, E144
Paraplegia	2	G81 G041, G820, G821, G822
Renal disease	2	N03, N052, N053, N054, N055, N056, N072, N073, N074, N01, N18, N19, N25
Cancer	2	C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C80, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C9451, C947, C95, C96
Metastatic cancer	3	C77, C78, C79, C80
Severe liver disease	3	K729, K766, K767, K721
HIV	6	B20, B21, B22, B23, B24

The effect of the antitussive use on ACEI therapy

In order to determine whether healthcare professionals follow the guideline and discontinue ACEI if ACEI induced cough is suspected, the duration of ACEI therapy was assessed. The ARB group was excluded in this analysis as well and the ACEI group

was further divided into the antitussive group which included subjects who received antitussives within 180 days after the ACEI initiation and non-use group which included subjects who did not received antitussives after the ACEI initiation. If ACEI was not discontinued and antitussives were prescribed in a patient with suspected ACEI-induced cough, the ACEI duration would be longer than the patient who were switched to ARB. Subjects with the history of antitussive use within 180 days before ACEI/ARB initiation were excluded in both groups to eliminate the effect of prior antitussive use (Figure 4).

The adherence rate of ACEI treatment was calculated with a follow-up period of 180 days to assess the long-term effect of antitussive treatment on ACEI therapy. If ACEI-induced cough is not detected and the patient is on ACEI and antitussives for a long duration, the patient might not be adherent to the ACEI therapy. ACEI therapy adherence was measured by the proportion of days covered, and the patients with the adherence rate of 80% or above was considered as adherent (Karve et al., 2009). The patients who discontinued the ACEI during the follow-up period were excluded to include chronic users only (Figure 4).

3. Statistical Analysis

A descriptive statistics of the study population were summarized and the differences between the groups were tested using the chi-squared test. A multivariate logistic regression model was used to determine predictors for the likelihood of antitussive treatment and hospital switching. In the logistic regression model, the dependent variable was the use of antitussives after ACEI or ARB initiation, and the measurements were presented as

multivariable-adjusted odds ratios with 95% confidence intervals. The differences in duration of ACEI therapy were analyzed using the independent t-test and the differences in ACEI therapy adherence were evaluated using the chi-squared test. *P*-value less than 0.05 was considered statistically significant. SAS version 9.4 (SAS Inc., Cary, NC) was used to perform the statistical analysis.

IV. Result

1. Antitussive Treatment after ACEI or ARB initiation

A total of 93,215 patients were initiated with either ACEI or ARB in 2004-2012, and 59,379 were selected after matching (Table 5). ACEI initiation was decreasing in time ($p < 0.001$), and ACEI was more likely initiated in Spring and Winter ($p < 0.001$) in tertiary or public hospitals ($p < 0.001$) on patients who have history of visiting more than one hospitals ($p < 0.001$). The patients with ACEI initiation generally had more comorbidities ($p < 0.001$). The subjects who were initiated with ACEI were more likely to use antitussives after the initiation ($p < 0.001$). Variables included in

Table 5. Characteristics of the ACEI and ARB initiators

	ACEI group (n=19,793)	ARB group, before matching (n=73,422)		ARB group, after matching (n=39,586)	
Variable	n (%)	n (%)	*P*-value	n (%)	*P*-value
Year			<.0001		<.0001
2004	4722 (23.86)	4667 (6.36)		2684 (6.78)	
2005	3682 (18.60)	5568 (7.58)		3064 (7.74)	
2006	2772 (14.00)	5599 (7.63)		3116 (7.87)	
2007	2703 (13.66)	6075 (8.27)		3351 (8.47)	
2008	2649 (13.38)	8691 (11.84)		4441 (11.22)	
2009	1274 (6.44)	11541 (15.72)		6029 (15.23)	
2010	876 (4.43)	10127 (13.79)		5711 (14.43)	
2011	687 (3.47)	11982 (16.32)		6271 (15.84)	
2012	428 (2.16)	9172 (12.49)		4919 (12.43)	
Season			<.0001		<.0001
Spring	5193 (26.24)	17378 (23.67)		9364 (23.65)	
Summer	4517 (22.82)	14727 (20.06)		7898 (19.95)	
Autumn	4144 (20.94)	16940 (23.07)		9162 (23.14)	
Winter	5939 (30.01)	24377 (33.20)		13162 (33.25)	
Hospital Type (ACEI/ARB)			<.0001		<.0001
Primary	10100 (51.03)	43894 (59.78)		23369 (59.03)	
Secondary	1630 (8.24)	7168 (9.76)		4057 (10.25)	
Tertiary	6623 (33.46)	19753 (26.90)		10604 (26.79)	
Public	1440 (7.28)	2607 (3.55)		1556 (3.93)	

Table 5. Continued

Variable	ACEI group (n=19,793) n (%)	ARB group, before matching (n=73,422) n (%)	*P*-value	ARB group, after matching (n=39,586) n (%)	*P*-value
History of antitussive use			<.0001		<.0001
No event	12810 (64.72)	60215 (82.01)		31620 (79.88)	
Event	6983 (35.28)	13207 (17.99)		7966 (20.12)	
History of visiting more than one hospitals			<.0001		<.0001
No event	3336 (16.85)	12458 (17.00)		6156 (15.55)	
Event	16457 (83.15)	60964 (83.00)		33430 (84.45)	
Antitussive use after ACEI/ARB initiation			<.0001		<.0001
No event	11111 (56.14)	56915 (77.52)		29682 (74.98)	
Event	8682 (43.86)	16507 (22.48)		9904 (25.02)	
Comorbidity			<.0001		<.0001
0	8776 (44.34)	36921 (50.29)		19049 (48.12)	
1	6240 (31.53)	22421 (30.54)		12318 (31.12)	
2	2709 (13.69)	8220 (11.20)		4708 (11.89)	
≥3	2068 (10.45)	5860 (7.98)		3511 (8.87)	
Variables included in matching					
Age group (years)			<.0001		0.8778
20-39	1468 (7.42)	6306 (8.59)		2928 (7.40)	
40-49	3639 (18.39)	16115 (21.95)		7278 (18.39)	
50-59	4994 (25.23)	20841 (28.39)		10002 (25.27)	
60-69	4970 (25.11)	15849 (21.59)		9993 (25.24)	
70-79	3470 (17.53)	10544 (14.36)		6988 (17.65)	
≥80	1252 (6.33)	3767 (5.13)		2397 (6.06)	
Gender			0.0784		0.9768
Male	10698 (54.05)	39168 (53.35)		21391 (54.04)	
Female	9095 (45.95)	34254 (46.65)		18195 (45.96)	
Area			<.0001		0.9966
Seoul	3471 (17.54)	15252 (16.36)		6937 (17.52)	
Metropolitan	5050 (25.51)	18070 (19.39)		10074 (25.45)	
City	7630 (38.55)	23499 (25.21)		15297 (38.64)	
Rural area	3642 (18.40)	16601 (17.81)		7278 (18.39)	
Income Level			<.0001		0.9953
≤20%	4185 (21.14)	16463 (22.42)		8329 (21.04)	
20%-40%	2994 (15.13)	10316 (14.05)		5966 (15.07)	
40%-60%	3359 (16.97)	11626 (15.83)		6762 (17.08)	
60%-80%	4026 (20.34)	14624 (19.92)		8052 (20.34)	
>80%	5229 (26.42)	20393 (27.78)		10477 (26.47)	
Insurance Type			<.0001		0.9802
Employee	10864 (54.89)	41235 (56.16)		21695 (54.80)	
Self-employed	7764 (39.23)	25982 (35.39)		15561 (39.31)	
Medical aid	1165 (5.89)	6205 (8.45)		2330 (5.89)	

matching such as age, gender, area of residence, income level, or insurance type showed no statistical significance, indicating that the matching was properly performed.

A multivariate logistic regression model assessed the likelihoods of the antitussive use after ACEI or ARB initiation (Table 6). After adjusting for the variables related to Anderson's behavioral model such as year and season of ACEI/ARB initiation, gender, area of residence, income level, insurance type, comorbidity, hospital type of ACEI/ARB initiation, history of antitussive use within 180 days before ACEI/ARB initiation, and history of visiting more than one hospitals, the ACEI group was significantly associated with the antitussive use after the initiation (OR 2.241; 95% CI 2.142-2.345). Patients from year 2011 (OR 1.091; 95% CI 1.003-1.181) had significantly higher odds of using antitussives after the initiation than those from year 2004. The likelihood of using antitussives is significantly higher among patients with the ACEI/ARB initiation in the summer (OR 1.239; 95% CI 1.167-1.315), autumn (OR 1.882; 95% CI 1.776-1.994) or winter (OR; 95% CI 1.595 1.512-1.683), compared to those with the initiation in the spring. Patients from city (OR 1.202; 95% CI 1.130-1.278) or rural area (OR 1.235; 95% CI 1.165-1.308) have significantly higher odds of using antitussives than those from Seoul. Patients who were initiated with ACEI/ARB in a primary hospital had significantly higher likelihoods of using antitussives than those who were initiated in a tertiary hospital (OR 1.226; 95% CI 1.170-1.285). The odds of using antitussive among patients with history of antitussive were significantly higher than those without the history (OR 5.739; 95% CI 5.507-5.982). Patients with history of visiting more than one hospitals had higher odds of using antitussives than those without the history (OR 1.284; 95% CI

Table 6. Multivariate Logistic Regression Model for Antitussive Use after ACEI/ARB Initiation

Variable	Before Matching		After Matching	
	OR	95% CI	OR	95% CI
Group				
ARB group				
ACEI group	2.311	2.218-2.408	2.241	2.142-2.345
Year				
2004				
2005	0.996	0.928-1.069	0.984	0.911-1.064
2006	0.993	0.923-1.068	0.996	0.918-1.080
2007	1.074	0.998-1.154	1.074	0.991-1.164
2008	0.904	0.842-0.971	0.937	0.864-1.015
2009	0.977	0.911-1.048	0.978	0.901-1.061
2010	1.052	0.980-1.130	1.063	0.979-1.156
2011	1.113	1.036-1.195	1.091	1.003-1.187
2012	0.963	0.893-1.038	0.986	0.901-1.079
Season				
Spring				
Summer	1.269	1.206-1.335	1.239	1.167-1.315
Autumn	1.875	1.786-1.969	1.882	1.776-1.994
Winter	1.577	1.507-1.651	1.595	1.512-1.683
Hospital Type (ACEI/ARB)				
Primary	1.194	1.148-1.242	1.226	1.170-1.285
Secondary	0.971	0.911-1.035	0.976	0.905-1.052
Tertiary				
Public	1.086	0.997-1.183	1.098	0.998-1.208
History of antitussive use				
No				
Yes	6.889	6.653-7.134	5.739	5.507-5.982
History of visiting more than one hospitals				
No				
Yes	1.214	1.154-1.278	1.284	1.207-1.365
Comorbidity				
0				
1	1.106	1.064-1.150	1.141	1.090-1.195
2	1.179	1.118-1.244	1.199	1.126-1.276
≥3	1.129	1.061-1.201	1.129	1.051-1.212
Age Group				
20-39				
40-49	1.025	0.953-1.102	1.039	0.948-1.138
50-59	1.192	1.112-1.278	1.215	1.114-1.326
60-69	1.583	1.475-1.699	1.602	1.469-1.747
70-79	1.646	1.526-1.776	1.608	1.467-1.762
≥80	1.182	1.073-1.301	1.155	1.032-1.293

Table 6. Continued

Variable	Before Matching		After Matching	
	OR	95% CI	OR	95% CI
Gender				
Male				
Female	1.250	1.209-1.294	1.302	1.250-1.355
Area of Residence				
Seoul				
Metropolitan city	1.009	0.957-1.064	1.038	0.971-1.110
City	1.239	1.178-1.303	1.202	1.130-1.278
Rural area	1.281	1.222-1.344	1.235	1.165-1.308
Income Level				
≤20%				
20%-40%	0.970	0.914-1.030	0.957	0.892-1.026
40%-60%	0.985	0.929-1.044	0.973	0.910-1.042
60%-80%	0.922	0.872-0.975	0.913	0.855-0.975
>80%	0.889	0.843-0.937	0.906	0.851-0.964
Insurance Type				
Employee				
Self-employed	1.033	0.997-1.070	1.005	0.965-1.047
Medical aid	0.500	0.458-0.546	0.503	0.449-0.564

OR = odds ratio; CI = confidence interval

1.207-1.365). The likelihoods of antitussive use among the patients on a medical aid is significantly less than those on employee insured (OR 0.503; 95% CI 0.449-0.564). For other variables, female gender, increasing age, and higher income level were significantly associated with the antitussive use.

2. Hospital Switching

For the analysis of hospital switching, patients who were initiated with ARB (n = 39,586) and patients without antitussive use after ACEI/ARB initiation (n = 11,111) was excluded. Among patients who were initiated with ACEI, 5,533 patients were prescribed with antitussives at different hospitals, and 3,149 patients were

Table 7. Characteristics of the patients who switched and did not switch hospitals

Variable	Switched (n=5,533) n (%)		Non-switched (n=3,149) n (%)		*P*-value
Year					<.0001
2004	1254	(22.66)	847	(26.9)	
2005	1021	(18.45)	626	(19.88)	
2006	810	(14.64)	467	(14.83)	
2007	807	(14.59)	469	(14.89)	
2008	628	(11.35)	338	(10.73)	
2009	377	(6.81)	163	(5.18)	
2010	283	(5.11)	109	(3.46)	
2011	207	(3.74)	87	(2.76)	
2012	146	(2.64)	43	(1.37)	
Season					0.1070
Spring	1322	(23.89)	696	(22.10)	
Summer	1120	(20.24)	679	(21.56)	
Autumn	1376	(24.87)	757	(24.04)	
Winter	1715	(31.00)	1017	(32.30)	
Hospital Type (ACEI)					<.0001
Primary	2404	(43.45)	2363	(75.04)	
Secondary	429	(7.75)	188	(5.97)	
Tertiary	2240	(40.48)	459	(14.58)	
Public	460	(8.31)	139	(4.41)	
Hospital Type (Antitussive)					<.0001
Primary	4990	(90.19)	2363	(75.04)	
Secondary	228	(4.12)	188	(5.97)	
Tertiary	218	(3.94)	459	(14.58)	
Public	97	(1.75)	139	(4.41)	
History of antitussive use					0.0247
No event	2607	(47.12)	1405	(44.62)	
Event	2926	(52.88)	1744	(55.38)	
History of visiting more than one hospitals					<.0001
No event	399	(7.21)	529	(16.80)	
Event	5134	(92.79)	2620	(83.20)	
Comorbidity					<.0001
0	2064	(37.30)	1407	(44.68)	
1	1854	(33.51)	1008	(32.01)	
2	941	(17.01)	436	(13.85)	
≥3	674	(12.18)	298	(9.46)	

Table 7. Continued

Variable	Switched n (%)		Non-switched n (%)		*P*-value
Age group (years)					0.0009
20-39	362	(6.54)	176	(5.59)	
40-49	889	(16.07)	529	(16.8)	
50-59	1341	(24.24)	864	(27.44)	
60-69	1612	(29.13)	833	(26.45)	
70-79	1058	(19.12)	567	(18.01)	
≥80	271	(4.90)	180	(5.72)	
Gender					0.0965
Male	2652	(46.08)	1451	(47.93)	
Female	2881	(53.92)	1698	(52.07)	
Area					0.1400
Seoul	938	(16.95)	496	(15.75)	
Metropolitan	2152	(38.89)	1263	(40.11)	
City	1412	(25.52)	843	(26.77)	
Rural area	1031	(18.63)	547	(17.37)	
Income Level					<.0001
≤20%	1026	(18.54)	637	(20.23)	
20%-40%	801	(14.48)	514	(16.32)	
40%-60%	962	(17.39)	590	(18.74)	
60%-80%	1139	(20.59)	634	(20.13)	
>80%	1605	(29.01)	774	(24.58)	
Insurance Type					0.1005
Employee	3254	(58.81)	1785	(56.68)	
Self-employed	2127	(38.44)	1262	(40.08)	
Medical aid	152	(2.75)	102	(3.24)	

prescribed with antitussives at the same hospitals (Table 7). The hospital switching was increased in time ($p < 0.001$). Patients who switched hospitals were least likely to be initiated with ACEI at the primary hospitals ($p < 0.001$), but most likely to choose primary hospitals to receive antitussive treatment ($p < 0.001$). Patients who switched hospitals were less likely to have history of antitussive use ($p < 0.0247$) but more likely to have history of visiting more than one hospitals ($p < 0.001$). Patients with hospital switch genereally had more comorbidities ($p < 0.001$) and higher income

(p < 0.001). No statistical difference was found in the season of ACEI initiation, gender, area of residence, and insurance type.

A multivariate logistic regression model assessed the likelihoods of the hospital switching (Table 8). After adjusting for the variables, in terms of the type of hospitals where the ACEI was initiated, the likelihood of the hospital switch is significantly lower for primary hospitals than tertiary hospitals (OR 0.069; 95% CI 0.057-0.083). On the other hand, in terms of hype of hospitals where the antitussives were first prescribed after the ACEI initiation, the primary hospitals were significantly more associated with the hospital switching than tertiary hospitals (OR 26.806; 95% CI 21.173-33.937). Patients with history of visiting more than one

Table 8. Multivariate Logistic Regression Model for Hospital Switching

Variable	OR	95% CI
Hospital Type (ACEI)		
Primary	0.069	0.057-0.083
Secondary	0.303	0.232-0.396
Tertiary		
Public	0.508	0.375-0.689
Hospital Type (Antitussive)		
Primary	26.806	21.173-33.937
Secondary	6.182	4.485-8.522
Tertiary		
Public	3.032	2.044-4.498
Year		
2004		
2005	1.058	0.911-1.227
2006	1.170	0.994-1.377
2007	1.128	0.959-1.326
2008	1.203	0.997-1.451
2009	1.265	0.999-1.603
2010	1.318	0.995-1.744
2011	1.171	0.842-1.629
2012	1.395	0.920-2.115

Table 8. Continued

Variable	OR	95% CI
Season		
Spring		
Summer	0.876	0.758-1.014
Autumn	0.864	0.746-1.000
Winter	0.906	0.790-1.040
History of antitussive use		
No event		
Event	0.924	0.843-1.014
History of visiting more than one hospitals		
No event		
Event	2.304	1.958-2.711
Comorbidity		
0		
1	1.079	0.959-1.214
2	1.162	0.989-1.363
≥3	1.111	0.922-1.340
Age group (years)		
20-39		
40-49	0.845	0.666-1.073
50-59	0.768	0.564-1.008
60-69	0.846	0.674-1.063
70-79	0.787	0.618-1.001
≥80	0.753	0.567-1.005
Gender		
Male		
Female	1.057	0.954-1.170
Area		
Seoul		
Metropolitan	0.963	0.829-1.118
City	0.932	0.796-1.091
Rural area	0.982	0.826-1.166
Income Level		
≤20%		
20%-40%	0.925	0.777-1.102
40%-60%	0.947	0.800-1.121
60%-80%	0.996	0.844-1.176
>80%	1.116	0.954-1.306
Insurance Type		
Employee		
Self-employed	0.946	0.853-1.049
Medical aid	0.884	0.625-1.250

hospitals also had significantly higher odds of hospital switching (OR 2.304; 95% CI 1.958-2.711). Other variables did not show statistical significance.

3. The effect of the antitussive use on ACEI therapy

For the analysis of the mean duration of ACEI therapy, 6,983 patients who used antitussives within 180 days prior to the ACEI initiation were excluded, and selected patients were divided into subgroups: antitussive group (n=3,755) and non-use group (n=9,055). The patients who were treated with antitussives after the ACEI initiation were on ACEI therapy longer than those who did not use antitussives (mean ± standard deviation (SD) 117.9 ± 80.4 days and 112.0 ± 84.6 days respectively; p = 0.0003) (Table 7).

For the analysis of the ACEI adherence, 5,888 patients who discontinued ACEI during the follow-up period of 180 days were further excluded, and the selected patients were divided into antitussive group (n=2,012) and non-use group (n=4,910). The adherence of chronic ACEI users with antitussive use was 46.1% whereas the adherence of those without antitussives was 49.5% (p = 0.0119) (Table 9).

Table 9. ACEI Therapy Duration and Adherence

	Antitussive Group	Non-use Group	*P*-value
ACEI Duration (mean ± SD, days)	117.9 ± 80.4	112.0 ± 84.6	0.0003
Adherence to ACEI (%)	46.1	49.5	0.0119

SD = standard deviation

V. Discussion

This is the first study that assessed the antitussive uses on the ACEI-induced cough using claim data in Korea. While ACEI, compared to ARB, can cause dry cough in significant number of patients, there are barriers for healthcare professionals for detecting the ACEI-induced cough in Korea. This study therefore hypothesized that the likelihood of antitussive use was higher among patients who were initiated with ACEI.

As expected, the initiation of ACEI was significantly associated with the likelihood of antitussive treatment (OR 2.241; 95% CI 2.142-2.345), and it is consistent with the previous findings (Vegter et al., 2010). Therefore it can be assumed that the ACEI-induced cough is not detected by the physicians or pharmacists or is treated with antitussives symptomatically, despite of the recommendation of the clinical guideline (Kim et al., 2014). It is also important to note that the number of patients who were initiated with ACEI decreased over time, which might suggest that physicians are aware of the potential ACEI-induced cough and avoid the problem by prescribing ARB instead. However, the likelihood of antitussive use did not change over time, with an exception of years 2011 (OR 1.091; 95% CI 1.003-1.181). The increase of likelihood of antitussive use in 2011 might be due to the implementation of "indicator linkage management system" by HIRA, which supervised hospitals from prescribing unnecessary antibiotics for patients with upper respiratory infection (Um, 2017). This policy might encourage physicians to prescribe antitussives rather than antibiotics.

The patients who were initiated with ACEI or ARB at a primary hospital were more likely to use antitussive than those

who were initiated at a tertiary hospital (OR 1.226; 95% CI 1.170-1.285). Surprisingly, patients who were initiated with ACEI at primary hospitals were less likely to switch hospitals to receive antitussive treatment than those who were initiated at tertiary hospitals (OR 0.069; 95% CI 0.057-0.083). In fact, among patients who were initiated with ACEI at primary hospitals, 49.6% were prescribed with antitussives at the same hospitals. However, patients who switched the hospitals were more likely to choose primary hospitals (OR 26.806; 95% CI 21.173-33.937). This may indicate that the patients who visited primary hospitals are treated symptomatically for ACEI-induced cough.

The patients with history of visiting more than one hospitals were more likely to use antitussives (OR 1.284; 95% CI 1.207-1.365), and more likely to switch hospitals (OR 2.304; 95% CI 1.958-2.711). It might be due to the viral infection caused by visiting different hospitals, but this may also indicate that switch hospitals or pharmacies makes harder for healthcare professionals to detect drug-induced adverse events. If a patient continue to use visit one hospital, a physician can easily detect whether a cough is induced by ACEI, and change the medication appropriately without prescribing antitussives. In contrast, if a cough patient with multiple prescribers presents, a physician is less likely able to detect the ACEI-induced cough, and thus treat symptomatically with antitussives.

The higher income level was associated with less likelihood of antitussive use (60%-80% of median: OR 0.913; 95% CI 0.855-0.975, >80% of median: OR 0.906; 95% CI 0.851-0.964). This is consistent with the literature that cough is more associated with patients with lower income (Ford, Forman, Moayyedi, & Morice, 2006). In contrast, patients on a medical aid have significantly less

likelihoods of using antitussive than those on a employee insured (OR 0.503; 95% CI 0.449-0.564). This might suggest that patients on a medical aid have low accessibility to the healthcare services and do not receive an appropriate treatment (Lee & Kim, 2015).

The patients who were initiated with ACEI or ARB in the summer (OR 1.239; 95% CI 1.167-1.315), autumn (OR 1.882; 95% CI 1.776-1.994) or winter (OR 1.595; 95% CI 1.512-1.683) were more likely to use antitussives than those who were initiated in the spring. In this study, antitussive use was followed for 6 months after the ACEI/ARB initiation. Therefore ACEI or ARB initiation in the spring, summer, autumn, or winter represents antitussive use in the summer, autumn, winter, or spring, respectively. Typically cough is known to be more common in the spring when the pollen level is high, or in the autumn and winter when the common cold is prevalent (Chung et al., 2008), and the result is consistent with the literature. The patients with history of antitussive use prior to the ACEI/ARB initiation had significantly higher odds of using antitussives after the initiation (OR 5.739; 95% CI 5.507-5.982). This might be due to the chronic cough which required antitussive treatment regardless of ACEI or ARB initiation. The female patients were more likely to use antitussives than male patients (OR 1.302; 95% CI 1.250-1.355). Since females are more sensitive to the cough reflux, they have increased risk of developing general cough as well as ACEI-induced cough (Chung et al., 2008; Vegter et al., 2010), which might caused higher antitussive uses. In terms of ages, all age groups that are older than 50 years were had higher likelihood of using antitussives than patients who are less than 40 years old (Table 6). It might be caused by diminished immune system due to aging (Castelo-Branco & Soveral, 2014). As for the comorbidity, patients

with one or more comorbidities were more likely to use antitussives (Table 6). Multiple comorbidities are known to be associated with the higher risk of cough (Song et al., 2013). Finally, patients from city (OR 1.202; 95% CI 1.130-1.278) or rural area (OR 1.235; 95% CI 1.165-1.308) have significantly higher likelihoods of using antitussives than those from Seoul. This may be due to the older population in such areas, which contributed to higher antitussive uses.

The mean duration of ACEI therapy can assess the effect of antitussive treatment on ACEI-induced cough. If ACEI was discontinued without prescribing antitussives in a patient with suspected ACEI-induced cough, the duration would be shorter than the patient who were treated with antitussives symptomatically for the ACEI-induced cough. In this study, the mean ACEI duration among patients who were treated with antitussives after the ACEI initiation was longer than those who did not use antitussives (mean ± SD 117.9 ± 80.4 days vs. 112.0 ± 84.6 days; $p < 0.001$). Also, the long-term ACEI therapy adherence was lower in patients who were treated with antitussives than those who did not use antitussives (46.1% vs. 49.5%, $p = 0.012$). These results are consistent with the study hypothesis and suggest that if ACEI is not switched to ARB due to the undetected ACEI-induced cough, the patients are on ACEI therapy longer than they should be, and the adherence to ACEI will be decreased, resulting in increased risk of hospitalization and mortality (Ho et al., 2008; Amin, Mukhopadhyay, Nathan, Napan, & Kelly, 2009). Thus the healthcare professional must pay close attention to the patients who were initiated with an ACEI, and incorporating a system to prevent the inappropriate antitussive prescription to the existing real-time National Drug Utilization

Review may be necessary.

A limitation of the study is that some health, behavioral, and environmental factors for the cough, such as smoking habits, allergies, or environmental status could not be evaluated since KNHIS NSC is primarily a medical claim data. It contains the partial health examination data of the subjects. Thus some of the confounding variables were not properly controlled. In addition, over the counter (OTC) antitussives were not evaluated in this study since KNHIS NSC do not include OTC medications. This may affected the number of patients who used antitussives prior to the ACEI or ARB initiation and after the initiation. For example, the result might be underestimated if patients used OTC to manage ACEI-induced cough without visiting physicians. In contrast, the result might be overestimated if patients used OTC before the initiation and afterwards visited hospitals more frequently for irrelevant coughs.

VI. Conclusion

This study found that the cough patients who were initiated with ACEI are often treated symptomatically with antitussives in Korea, instead of discontinuing ACEI. The antitussive treatment decreased the ACEI therapy adherence. A preventive approach from inappropriate prescription of antitussives secondary to ACEI-induced cough would be necessary.

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국문초록

배경

안지오텐신 전환 효소 억제제(Angiotensin-converting enzyme inhibitors, ACEI)는 특히 아시아 인들 사이에서 마른 기침을 유발할 수 있다. 여러 진료 지침에 따르면 ACEI로 인한 기침이 발생할 경우 복용을 중단하고 안지오텐신 수용체 차단제(Angiotensin Receptor Blockers, ARB)로 전환하도록 권고됨에도 불구하고 전문가가 ACEI로 인한 기침을 감지하지 못하면 환자는 불필요하게 진해제를 처방받을 수 있다. 따라서 이 연구의 목적은 ACEI 치료의 개시가 ARB 개시와 비교하여 진해제 사용의 가능성에 미치는 영향과 진해제 사용이 ACEI 치료 기간과 순응도에 미치는 영향을 조사하는 것이다.

방법

2002년부터 2013년까지 국민건강보험공단 표본코호트 데이터베이스가 사용되었다. 성인 중 2004년에서 2012년 사이에 ACEI 또는 ARB 치료를 개시한 환자를 선택하여 ACEI 그룹과 ARB 그룹을 propensity score에 의해 매칭하였다. 진해제 처방에 영향을 줄 수 있는 공변량은 앤더슨 행동 모형을 통하여 선택되었다. 진해제 사용 가능성과 요양기관 변경은 다변량 로지스틱 회기분석으로 검증되었고, ACEI 치료 기간의 차이는 t-검정이 사용되었으며, 약 처방일수의 비(Proportion of Days Covered, PDC)로 계산된 ACEI 치료 순응도의 차이는 카이 제곱 검정이 사용되었다.

결과

2004년에서 2012년 사이에 ACEI를 개시한 환자 19,793명과 ARB를 개시한 환자 39,586명이 매칭되었다. ACEI의 개시는 진해제 사용과 통계적으로 의미있는 상관성을 보였다 (OR 2.241; 95% CI 2.142-2.345). ACEI 처방 기관의 경우 1차 병원이 3차 병원보다 요양기관을 변경할 가능성이 의미있게 낮았으나 (OR 0.069; 95% CI 0.057-0.083), 진해제

처방 기관의 경우 3차 병원에 비해 1차 병원을 선택할 가능성이 의미있게 높았다 (OR 26.806; 95% CI 21.173-33.937). ACEI 개시 이후 진해제를 처방받은 환자는 그렇지 않은 환자에 비해 더 장기간 ACEI를 복용하였다 (평균 ± 표준편차 117.9 ± 80.4 days vs. 112.0 ± 84.6 days; p < 0.001). ACEI 복약순응도는 개시 이후 진해제를 사용한 환자가 그렇지 않은 환자보다 더 낮았다 (46.1% vs. 49.5%, p = 0.012).

결론

본 연구에서는 ACEI를 개시한 기침환자에게 대증요법으로 진해제 처방을 받는 경향이 큰 것으로 나타났으며 진해제 사용은 ACEI의 복약순응도를 감소시키는 것으로 나타났다. 따라서 기존의 실시간 약물 남용 검토 (Drug Utilization Review) 시스템에 부적절한 진해제 처방을 보완하기 위한 방안을 검토해야 할 필요성이 있다.

주요어 : 안지오텐신 전환 효소 억제제, 기침, 진해제
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