The impact of the reformed pricing system and new guideline for antihypertensive drugs on utilization and expenditures in Korea

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ABSTRACT

The impact of the reformed pricing system and new guideline for antihypertensive drugs on utilization and expenditures in Korea

Background: Increases in pharmaceutical expenditures constitute a major issue, and in response, the Korean government has reformed the drug pricing system and adopted new guideline for prescription and reimbursement. These policies were intended to reduce drug prices and restrict reimbursement from inappropriate prescriptions.

Objectives: The present study was conducted to identify the effects of the new pricing system and new guideline for antihypertensive drugs on utilization and expenditures in Korea.

Methods: Decomposition analysis was conducted for the macro perspective and segmented regression analysis was for stochastic analysis with 54,295 subjects which were only with primary hypertension in the data. National patient sample data of Health Insurance Review & Assessment Service was used in both analyses. The study period was from March 2011 to December 2013. The dependent variables were daily drug utilization, prescribing days, average number of drugs per month, percentage of original drugs per prescription, drug overutilization and prohibited combinations for antihypertensive drug utilization, and antihypertensive drug costs, antihypertensive drug cost per prescribing day, outpatient medical costs whose primary diagnosis was primary hypertension(I10-I13) for expenditures.

Results: The results of decomposition analysis indicated that total pharmaceutical expenditures decreased by 9.8% after implementation of the pricing policy, and by an additional 5.9% after the guideline was adopted. Following the implementation of the new pricing policy, the quantity index (-3%) and expenditures (-25%) of price-reduced drugs decreased, but the quantity (2%) and expenditures(5%) of not price-reduced drugs increased. The expenditures in both groups (price-reduced: -7%; not price-reduced: -5%) decreased without increasing quantities after the new guideline was implemented. The indexes of therapeutic choice in both groups increased slightly following both policies. These policies could not control expensive drugs such as angiotensin receptor blockers and calcium channel blockers.

From the results of segmented regression, these policies saved approximately USD 5.47 (29.1%) of sum of antihypertensive drug costs and outpatient medical cost, and USD 4.22 (28%) of antihypertensive drug costs in December 2013 compared to March 2012. The effect of the new guideline reduced expenditures more than the new drug pricing system in a segmented regression analysis. Original drug utilization rates did not change significantly as a function of the policies. Drug overutilization and prohibited combinations increased after the new pricing system, and decreased after the new guideline.

Conclusions: Policymakers must consider the side effects and the comprehensive effects when controlling drug price directly. The policies saved money, but there were some side effects caused by the new pricing system. The guideline which is a kind of soft regulations was more effective, more reliable, less side effects than the direct cost control.

Key words: antihypertensive drug, pricing policy, guideline, utilization, expenditures

I. Introduction

Health insurance in South Korea is controlled exclusively by the government under a single-payer system[1]. It provides universal healthcare coverage for the country's entire population. As in most countries, controlling increases in total health expenditure is a major concern. Total health expenditures in South Korea accounted for 7.4% of GDP in 2011. It ranks 27th among the 34 OECD (Organisation for Economic Co-operation and Development) countries[2]. Its percentage of total health expenditure is lower than the OECD average of 9.3%, but the increase in its health expenditure rate is 9.3%, which is higher than that of most OECD countries.

South Korean pharmaceutical expenditures are among the fastest growing in the world among OECD countries, behind only Chile. The average annual pharmaceutical expenditure per capita increased by 9.8% between 2000 and 2009, and by 5.4% between 2009 and 2011. In 2011, South Korean pharmaceutical expenditures comprised 20.2% of total health expenditures.[2] The South Korean pharmaceutical expenditure rate was higher than the OECD average rate of 16.4%.

There are two primary reasons for the pharmaceutical expenditure increase, namely, the institutional framework and population effects. Previous studies have reported that the drug pricing policy led to increases in pharmaceutical expenditures.[3,4] Further, the rapid growth of the elderly population and the increase in chronic diseases, such as hypertension, have led to such increases.[5] Hypertension is the most prevalent chronic disease in Korea, with 29.0% of individuals over 30 years old affected in 2012.[6] Expenditures for antihypertensive drugs were approximately USD 800 million in 2012, accounting for 38.54% of cardiovascular drug expenditures.

In order to prevent further increases in pharmaceutical expenditures, pharmaceutical reforms that separated drug prescription and dispensing were enacted in 2000.[7] The positive-list system was implemented to replace the negative-list system in 2006.[8,9] To reduce rebate-related expenses, anti-rebate legislation law was established in 2010.[3]

In April 2012, the Korean government reformed the drug pricing system and reduced the prices of existing drugs.[10] The Korean government wanted to reduce pharmaceutical expenditures and increase the rate of generic drug utilization by reducing the price gap between generic and original drugs. The prescription and reimbursement guideline for antihypertensive drugs was introduced in January 2013 to control drug over utilization and improper prescriptions because primary physician's blood pressure control was poor in Korea.[11] However, the effects of drug price reduction and the new guideline on pharmaceutical expenditures were not identified. Accordingly, the objective of this study was to identify the effects of policy adoption on pharmaceutical expenditures.

II. Objectives

The purpose of this study was to examine the impact of the new pricing system and the new guideline for antihypertensive drugs on utilization, and expenditure.

The detailed objectives of this study were as follows:

(1) To analyze the effects of the reformed pricing system and the new guideline on the growth of pharmaceutical expenditures.

(2) To analyze the effects of the reformed pricing system and the new guideline on utilization, as measured by daily drug utilization, prescribing days, percent of original drugs remaining, drug overutilization, and prohibited combinations.

(3) To analyze the effects of the new pricing system and the new guideline on expenditure, as measured by outpatient medical costs, antihypertensive drug costs, and total expenditures.

III. Study Background

1. Regulating pharmaceutical expenditures

Govenments do not regulate markgets, but they do pharmaceutical market. It is because of access, quality, and cost problems. Governments ought to guarantee patient access and safety and effectiveness of drugs, improve the quality of care, and control costs[12]. Among these, the cost regulating is the focus of this study.

To control pharmaceutical expenditures, a target of policy for subjects will be pharmaceutical companies, consumers, physicians, pharmacists, wholesale dealers. A target of policy for process should be defined. Prescription, dispensing, taking medicines, reimbursement, distribution, production, and patenting stage can be targeted by a policy.[13] Governments usually establish a policy which targets on single or multiple subjects/process.

There are two way to regulate pharmaceutical expenditures. Based on Expenditure = Quantity x Price, policies for pharmaceutical expenditures usually affect drug prices or provide regulations for the quantity of drugs. Many countries implemented various drug pricing polies to control pharmaceutical expenditures.

The drug price control policy targets at different components of drug prices such as wholesale price, retail price, tax, and reimbursement prices; generally, the effects of a drug pricing policy are divided into direct effects on pharmaceutical expenditures and indirect effects on the changing of drug prescription behaviors.[14] The changing of drug prescription behaviors as a function of a drug pricing policy depends on who is making decisions on the selection and prescribing of drugs.[15] Physicians usually select drugs and

do not consider cost effectiveness, and they prefer to prescribe original drugs,[16,17] even though all generics have passed bioequivalence tests and the substitution of generic antihypertensive drugs does not lead to clinical problems.[18]

To control the quantity of drugs is related to quality. Healthcare policy makers usually consider good prescribing behavior to restrict unnecessary drug utilization.[12] Misuse, overuse, or underuse of drug utilization may cause an increase in pharmaceutical expenditures and negative health outcomes.[19] The purpose of restriction policy is to reduce unnecessary expenditures by restricting reimbursements and inducing the rational use of drugs. Restricting reimbursement may be a powerful method to change physician behavior in Korea. Some physicians may switch drugs, prescribe underuse of drugs, or charge for applying for exemptions as unintended consequences of policies.[20]

Wittermark et al.[21] classified pharmaceutical policy into traditional and soft. Traditional regulations are described as ‘four Es’:Education, Engineering, Economics, and Enforcement.[22] However, the four Es’s have strengths and limitations (Table 1). Three modes of soft regulations are standardization, monitoring and agenda setting. These are voluntary and not connected to punishment (Table 2). The soft regulations have recently introduced. The disadvantages of soft regulations are not always sufficiently effective, but they are effective without spending extra money. Evidences of soft regulations in pharmaceutical policies are few, the effects are needed to be identify.

In these perspectives, this study aimed to identify policy effects of between price and quantity, and between traditional and soft regulations. The new pricing policy for price and traditional regulations, and the new guideline for quantity and soft regulations were examined.

Table 1. Explanation of the 'four E'

Measure	Explanation	Strengths and limitations
Education	Range from simple distribution of printed material to more intensive strategies such as educational outreach visits by trained facilitators, monitoring of prescribing against agreed guidance with further interventions if required or various consensus processes.	Only a modest effect unless combined with other strategies. Simple diffusion or dissemination of printed materials and didactic educational meetings may influence professionals' awareness and knowledge but they seldom change behavior. More intensive strategies involving more than one approach may be more effective, especially given the idiosyncratic nature of prescribing; however, until recently, few studies have reported whether the benefits including savings achieved outweigh the costs of implementing the strategies
Engineering	Refers to organizational or managerial interventions. Structured programs for the introduction of new drugs.	May be effective in removing barriers to change, since it is known that the effectiveness of quality improvement initiatives is to a great extent influenced by the organizational context. However, they may be ineffective if there is poor leadership and poor processes. In addition, pharmaceutical companies may well seek other ways to influence prescribing to achieve their revenue goals unless adequately addressed
Economics	Include changes in insurance and reimbursement systems, patient co-payment including tier levels, positive and negative financial incentives for physicians and rebate schemes for over-prescribing of agreed drugs	Have been shown to be effective in moderating the annual increase in drug expenditure and in some cases reducing this. However, the long-term impact on expenditure as well as the impact on the quality of care subsequently provided have been less studied
Enforcement	Include regulations by law such as mandatory generic substitution at pharmacies.	May seem a suitable method in policy making since it is easier to implement and may be less expensive to operate than other measures. However, whilst effective in regulating the availability of medicines or their prescribing with, for instance, positive lists or sub-population restrictions, enforcement may not be equally effective in regulating human behavior; like all people, physicians and patients may find ways to bypass the regulations, diminishing the effects of these interventions in reality, unless addressed with strict controls.

Source: Wittermark et al.[21]

Table 2. Modes of soft regulation

Soft regulation	Associated activities
Standardization	Involves the development of potential activities or advice for others regarding what they should undertake. Formally, at least, these regulations are voluntary and include large elements of self-regulation and co-regulation.
Monitoring	Comprises various forms of scrutiny. Audits, evaluations, reporting and accounting systems as well as more general assessments, comparisons and rankings have expanded and become widespread in healthcare; this will grow.
Agenda setting	Expert groups exert their influence by organizing arenas, networks and conferences around certain issues. Important topics of these meetings are to discuss the standards and the results of any audits undertaken. Such activities are widespread in, for instance, Germany, Sweden and the UK.

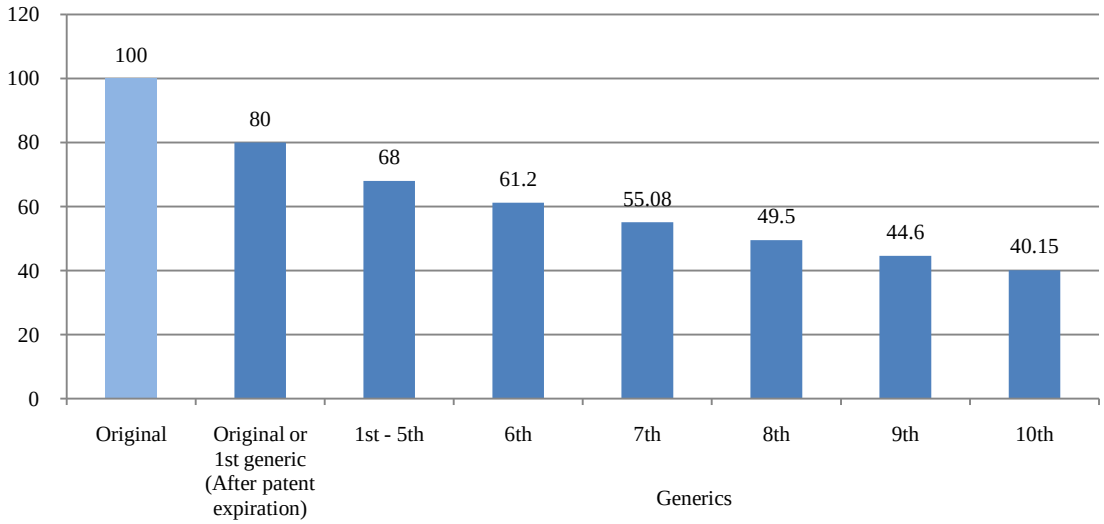
Source: Wittermark et al.[21]

2. The reformed drug pricing system in Korea

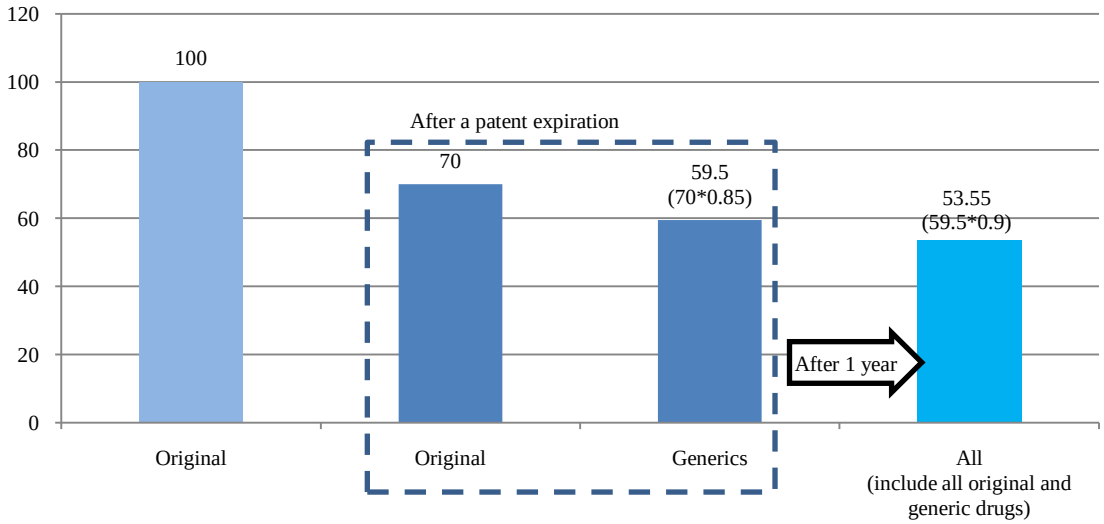
The previous pharmaceutical pricing system in Korea used orders to determine the price of each generic drug when it was listed. This type of pricing policy resulted in a lack of competition in terms of price and quality. The Korean government then suggested that drugs composed of the same ingredients should have the same price (53.55% of the original price) starting in April 2012 (Ministry of Health and Welfare notification 2011-176). In addition, the Korean government facilitated research and development among pharmaceutical companies by allowing their drugs to be priced higher (from 53.55% to 68% of the original price). To help bring generic drugs onto the market sooner, the prices of original drugs dropped from 80% to 70% of the price while under patent protection until one year following patent expiration. The price of the first generic drug is currently 59.5% of the price of the original drug, while it was 68% under the old system. These rules were applied to 13,184 listed drugs, and the prices of 6504 drugs were reduced. This led to a 14.2% reduction in the price of listed drugs (Figure 1).[23]

The Korean government published the goals of the new pricing system as follows: to reduce pharmaceutical expenditures, to increase accessibility of drugs, to decrease the burden of health insurance premiums, to block rebate activities, and to improve competitiveness among Korean pharmaceutical companies.[24]

Currently, there is one study on the new pricing system in Korea. Kim[25] reported the effect of the new pricing system on competition among generic medicines. As a result, pharmaceutical expenditures decreased, and the market share of generic drugs decreased by 0.03%.



a. Drug prices before April 2012.



b. Drug prices after April 2012

Figure 1. Estimated drug prices before and after policy change

There are many variations for drug price regulations; direct cost control. Direct cost control, use of international price comparisons, profit controls, reference pricing and free pricing. This new pricing system is the direct cost control policy.

Recent previous studies about price regulations are displayed in Table 3.

Kwon et al.[26] identified the effects of price cut for anti-hyperlipidemic agents. There were three rounds of price cut, but monthly drug expenditures increased steadily though it was not significant. The expenditure of not price-reduced drugs increased more than decline of priced reduced drugs.

In the study of Godman et al.[27], the drug price reduction policy was identified. Norway government reduced the drug prices only for generics, not for original. It led to increase use of generic drugs and to decrease pharmaceutical expenditures.

Sood et al.[28] examined price regulations on pharmaceutical revenues. Most of developed countries already had drug price regulation. In those cases, to adopt new regulations had a smaller impact on costs. However, implementing new regulations in unregulated market such as USA could greatly reduce pharmaceutical revenues.

Aaserud et al.[14] reviewed 11 articles of reference pricing and index pricing. In the cases of British Columbia, and Canada, reference drug pricing could reduce drug expenditures because of inducing a shift in drug use to cheap drugs. There were no evidence of adverse effects on health outcome and healthcare utilization.

Table 3. Recent previous studies for drug pricing regulations

Study	Regulations	Results
Kwon et al.[26]	Price-reduction policies for anti-hyperlipidemic drugs	Despite price cuts, monthly drug expenditures increased by USD 523,726 after the third intervention. The trend in volume increased consistently, but not significantly.
Godman et al.[27]	Changes in the pricing policies for generics and original drugs.	Utilization of generic simbastatin increased 15%. A 55% decrease in statin expenditure between 2004 and 2009. This reduction, coupled with low prices for generics as a result of recent pricing policies, resulted in proton pump inhibitors expenditure decreasing by 27% during the same period despite again appreciably increased utilization.
Sood et al.[28]	Analyzed the pharmaceutical regulations in nineteen developed countries from 1992 to 2004.	To adopt new regulations on some regulations had a smaller impact on costs. However, implementing new regulations in unregulated market could greatly reduce pharmaceutical revenues.
Aaserud et al.[14]	Review for effects of reference pricing, other pricing, and purchasing policies	Reference drug pricing can reduce drug expenditures by inducing a shift in drug use towards less expensive drugs. No evidence of adverse effects on health and no clear evidence of increased health care utilization.

3. The guideline for antihypertensive drugs

As expenditures for antihypertensive drugs have increased, the Korean government examined textbooks, guidelines, reimbursement evaluations, and research papers to establish set prescription and reimbursement guideline for antihypertensive drugs. The guideline indicate when to prescribe antihypertensive drugs and whether drugs should be used alone or in conjunction with another therapy. This guideline took effect in January 2013 (Table 4) (Ministry of Health and Welfare notification, 2012-155).

The effects of restriction of reimbursement could reduce pharmaceutical expenditures, and there was no evidence of spillover to utilization of other healthcare systems.[20] Previous studies on the restriction of antihypertensive drug reimbursement are shown in Table 5.

Wettermark et al.[29] evaluated the initial effects of a reimbursement restriction on prescription patterns in Sweden. Sweden implemented a reimbursement restriction on antihypertensive treatments. The restriction focused on subjects (e.g., pregnant woman) or combinations and side effects. The total expenditure decreased by 4.7% (€73 million) in 2008 compared to 2007. However, no confounders were adjusted, and health outcomes were not identified.

Fischer et al.[30] examined the effect of the restriction of angiotensin receptor blockers (ARBs) on drug use, as the increased use of ARBs led to pharmaceutical expenditures. Thus, Medicare introduced prior authorization (PA) to reduce the use of ARBs. In PA, physicians should submit relevant clinical information in order to prescribe ARBs. There were two types of policy groups. One was to recommend use of angiotensin-converting enzyme inhibitors (ACEIs) instead of ARBs. The other was to choose drugs from a

preferred list in place of ARB. Policy effects showed a significant decrease in ARB usage of 1.6% in ACEI groups.

Kahan et al.[31] conducted a longitudinal analysis of the policy examined by Fischer et al.[30] The number of submitted pieces of clinical information on ARB prescriptions was 961 in December 2007, which decreased to 494 after policy implementation. However, it increased to 984 in December 2008. The use of ARBs showed a long-term increase after policy implemented. The authors concluded that the policy was an effective limited-duration strategy.

Fretheim et al.[32] identified the effects of mandatory prescribing of thiazides for newly treated, uncomplicated hypertension by using interrupted time-series analysis. This policy could reduce by USD 0.72 million of pharmaceutical expenditures in the first year, but this savings on pharmaceutical expenditures were modest.

Green et al.[20] conducted systematic review for effects of restrictions on reimbursement. Restrictions on reimbursement of selected medications can decrease pharmaceutical expenditures without increasing the use of other health services. Reimbursement rules for drug use for secondary prevention can increase accessibility. The effects on health outcomes were inconclusive. The authors concluded that policy makers need to consider evidence and side effects about the effects on health outcomes.

Table 4. Prescription and reimbursement guideline for antihypertensive drugs

Hypertensive agents administered to hypertensive patients without comorbidity are allowed under the following conditions and reimbursement is provided if the conditions below are met.
Prescription and reimbursement guideline for antihypertensive drugs

A. Time for administering drugs.

1) If systolic blood pressure is over 140 mmHg or diastolic blood pressure is over 90 mmHg, administration of drugs is allowed.
2) Patients without risk factors for cardiovascular disorders should be advised to improve lifestyle first.

B. Rules for drug administration.

1) Type 1 hypotensive agents are administered first. If systolic blood pressure is over 160 mmHg or diastolic blood pressure is over 100 mmHg, type 2 hypotensive agents can be administered instead of type 1 hypotensive agents.
2) Even after hypotensive agents have been administered, if systolic blood pressure is over 140 mmHg or diastolic blood pressure is over 90 mmHg, various kinds of hypotensive agents can be administered. If you use four or more than four different types of drugs, a written statement justifying the prescription is necessary and the action will be allowed selectively.
3) The following combinations are not recommended. If you do decide to use them, only cases for which a valid reason is provided are allowed.
   a) Diuretic + α blocker
   b) β blocker + ACE inhibitor
   c) β blocker + angiotensin II receptor antagonist
   d) angiotensin-converting-enzyme inhibitor + angiotensin II receptor antagonist
(4) Drugs consisting of the same ingredients are administered once. The administration of compounds is considered to be the same as administering drugs that are components of the compounds.

※ Target patients: Hypertension patients without comorbidity, as follows.

- Cardiovascular diseases: angina pectoris, myocardial infarction, left ventricular hypertrophy, heart failure, ischemic heart diseases
- Cerebrovascular diseases, chronic kidney diseases (including proteinuria), diabetes, peripheral blood vessel diseases.

Table 5. Previous studies about the effect of guideline on antihypertensive drugs

Study	Objectives	Results
Wettermark et al.[29]	To identified the restrictions for combinations and specific subjects on total expenditures.	Total expenditures: -4.7% in one year
Fischer et al.[30]	Medicare prior authorization restricted to use ACEI or other drugs from a preferred drug list instead of ARBs. Physicians have to submit clinical information when use ARBs. This study identified the effects of restriction on use and spending of ARBs.	ARB use and spending decreased successfully in the group to use ACEIs. - ARB use: level effect: -1.6%; slope effect: -1.3% - ARB spending: level effect: -1.0%; slope effect: -0.7% It was not successful in the group to use other drugs from a preferred drug list.
Kahan et al.[31]	To identify the effects of Medicare prior authorization on use of ARBs.	ARB use declined by 48.6% after policy implementation, but rose 31.8% again after a year.
Fretheim et al.[32]	To identiy the effects of mandatory prescribing of thiazides for newly treated, uncomplicated hypertension on expenditures.	This policy could reduce by USD 0.72 million of pharmaceutical expenditures in the first year
Green et al.[20]	To determine the effects of restricting the reimbursement of selected medications on drug use, healthcare utilization, health outcomes and expenditures.	Restrictions on reimbursement of selected medications can decrease pharmaceutical expenditures without increasing the use of other health services. Reimbursement rules for drug use for secondary prevention can increase accessibility. The effects on health outcomes were inconclusive.

ARB: angiotensin II receptor antagonist

ACEI: angiotensin-converting-enzyme inhibitor

4. Decomposition analysis

Decomposition analysis is a well-known method in various fields.[33] It is used to understand the macro effects of policies. To summarize the decomposition analysis in pharmaceutical expenditures from 1990s, Gerdtham et al. evaluated drug expenditure several times by decomposing the growth in the relative price, the quantity of drug consumed, and residual with using World Health Organization (WHO) defined daily dose (DDD)[34,35]. Chernew et al.[36] used it to conduct a deterministic analysis of pharmaceutical expenditure increases in different types of health plans. Addis and Margrini[37] used same equation to Gerdtham et al.[34] with DDD. To use DDD in a decomposition analysis allows to compare among countries and across different formularies. In this study, Gerdtham et al.[34] and Addis and Margrini[37]'s method were used.

Framework

Decomposition analysis expresses the growth of pharmaceutical expenditure from the base period to the target period. There are three components in decomposition analysis, namely, an index of quantity growth, Laspeyres index, the therapeutic choices, which are displayed in Equation 1 as (a), (b), and (c), respectively.

$$\text{The growth of expenditure} = \frac{\sum P_i^1 Q_i^1}{\sum P_i^0 Q_i^0} = (a)\ \frac{\sum Q_i^1}{\sum Q_i^0} \times (b) \frac{\sum P_i^1 Q_i^0}{\sum P_i^0 Q_i^0} \times (c) \frac{\frac{\sum P_i^1 Q_i^1}{\sum Q_i^1}}{\frac{\sum P_i^1 Q_i^0}{\sum Q_i^0}} \cdots (1)$$

Q_i : quantity of drug utilization for each drug by adjusting DDD.

DDD : Defined daily doses(DDD). It is defined by WHO

P_i : price per DDD for each drug.

All quantity of drug are adjusted DDD to calculate an index of quantity growth.[38]

$$Q_i = q_i / DDD_i \cdots (2)$$

In Equation 2, q_i represents the utilization quantity for each drug i from the reimbursement data. DDD_i represents the DDD per each drug, and Q_i is a quantity for each drug adjusted for DDD. As quantities are expressed in terms of DDD, prices must be described in an identical manner.

$$P_i = E_i / Q_i \cdots (3)$$

P_i Represents an price per DDD for each drug *i* (Equation 3).

The Laspeyres index represents the price fluctuation index per DDD from the base period to the target period weighted by the base period volume. It shows the pure price change between two periods.[39]

The mix movement index—or residual effect—represents the ratio of the average price of the target period and the average price of the base period referring to the target period. If the index is greater than one, the average price per DDD increased as a function of the change in the mix of drugs, indicating that hospitals select more expensive drugs in the target period than in the baseline period.

5. Segmented regression analysis in interrupted time series analysis

Interrupted time series analysis is the strong quasi-experimental research for evaluating policy effects. In interrupted time series analysis, data are collected at time point such as day or month. After the intervention time points are set, the effect of interventions can be evaluated before and after interventions.[40] As kinds of interrupted time series analysis, auto-regressive integrated moving average(ARIMA) and its variations are popular, and segmented regression analysis is widely used in healthcare policy area.

Segmented regression analysis is able to be used for evaluating the effects in randomized trial or a natural experiment. The strength and its limitaions are showed in Table 6.

Table 6. Strength and limitation of segmented regression analysis

Strength	Limitation
In contrast to cross-sectional observational studies, segmented regression analysis allows to control for prior trends in the outcome and to study the changes in response to an intervention. Segmented regression analysis can be conducted without a control group. Able to display the dynamics visually.	The assumption of linearity. As data aggregated by time points, sometimes some independent variables could not be adjusted.

Source: Wagner et al.[41]

For overcoming the limitation of segmented regression analysis, Sen et al.[42] tested square terms of time related variables and applied the repeat measured individuals. As the basic formula of segmented regression analysis is in Equation 4.

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention\_1_t +$$

$$\beta_3 \times time\ after\ intervention\_1_t + \beta_4 \times intervention\_2_t +$$

$$\beta_5 \times time\ after\ intervention\_2_t + e_t \cdots (4)$$

Y: dependent variables

t: time period

time: a continuous variable started at baseline

intervention_1: a binary variable (0 before; 1 after *intervention_1*)

time after intervention_1: a continuous variable started after *intervention_1*

intervention_2: a binary variable (0 before; 1 after *intervention_2*)

time after intervention_2: a continuous variable started after *intervention_2*

e: the error term

The structure of data for segmented regression is displayed in Table 7. Based on the Equation 1 and Table 7, Sen et al.[42] improved the equation as Equation 5.

Table 7. Structure of data for segmented regression

Patient ID	Costs($)	Time (Month)	Intervention_1	Time after intervention_1	Intervention_2	Time after intervention_2
1	9.5	1	0	0	0	0
1	8.8	2	0	0	0	0
1	9.0	3	0	0	0	0
1	8.9	4	1	1	0	0
1	8.8	5	1	2	0	0
1	9.0	6	1	3	0	0
1	8.8	7	1	4	0	0
1	8.6	8	1	5	1	1
1	8.7	9	1	6	1	2
1	9.2	10	1	7	1	3
1	8.4	11	1	8	1	4

$$Y_{it} = \beta_0 + \beta_1 \times time_t + \beta_2 \times time^2{}_t + \beta_3 \times intervention\_1_t +$$

$$\beta_4 \times time\ after\ intervention\_1_t + \beta_5 \times time\ after\ intervention\_1^2{}_t +$$

$$\beta_6 \times intervention\_2_t + \beta_7 \times time\ after\ intervention\_2_t +$$

$$\beta_8 \times time\ after\ intervention\_2^2{}_t + X_{it} + e_{it} \cdots (5)$$

i: each patient

X: independent variables

The squared term is used to adjust the possibility that the trends are non-linear. Repeat measured individuals are adjusted. In this study, segmented regression analysis is used for evaluating the effects of policies with the methods in Wagner et al.[41] and Sen et al[42] only without the squared term because the number of time points in this study are not so long.

IV. Material and Methods

1. Decomposition analysis

Study data

This study used the National Patient Sample (NPS) data from Health Insurance Review and Assessment Service (HIRA).The sample included 57,150 subjects which were 1% of the randomly sampled from hypertensive patients. As the period between after the new pricing system and before the new guideline was 9 months, the study period investigated was from July 2011 to September 2013. The study period was classified into three categories, namely, before the new pricing system (July 2011–March 2012), after the new pricing system and before the new guideline (April 2012–December 2012), and after the new guideline (January 2013–September 2013)(Figure 2).

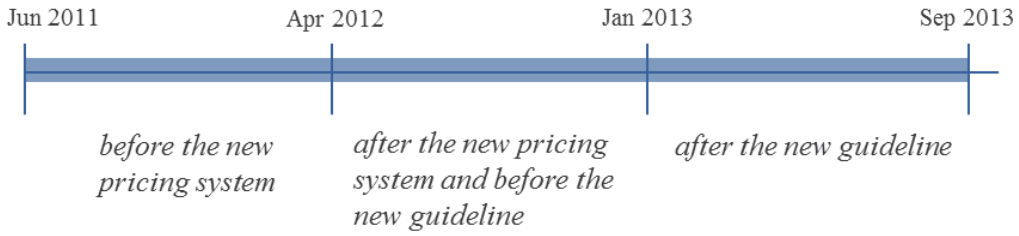


Figure 2. Study period for decomposition analysis

Drug classification and Statistical analysis

All antihypertensive drugs was classified into the following types: alpha blockers, beta blockers, calcium channel blockers (CCBs), diuretics, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEI), vasodilators, cytidine

diphosphate choline (CDP-choline), and combinations.

As some drugs were not applied to the new pricing policy, sub-group analyses were conducted to determine whether a drug's price decreased. In the case of antihyperlipidemic agents for price cuts in 2009 and 2010, total pharmaceutical expenditure was increased because of expenditures of not price-reduced drugs increased more than decline in expenditures of price-reduced drugs.[26] It is needed to identify whether the same phenomenon appeared for antihypertensive drugs.

Decomposition analysis was used to identify the growth of pharmaceutical expenditure from the base period to the target period.

2. Interrupted time series analysis

As decomposition cannot identify personal effects, interrupted time series analysis was used for stochastic analysis.

Data and study population

This study used HIRA reimbursement data, which were the same data that were used for the decomposition analysis. The study period was from March 2011 to December 2013. NPS data included subjects who had visited healthcare institutions for hypertension. Only patients with primary hypertension were included. Inpatient and outpatient data with a major diagnosis from I10 to I13 were included. A total of 54,295 subjects were included in this study (Figure 3). Data from January and February 2011 were excluded because of missing utilization data. In this analysis, the guideline began in February 2013, as there was a 1-month lagged effect after implementation of the new guideline. (Figure 4).

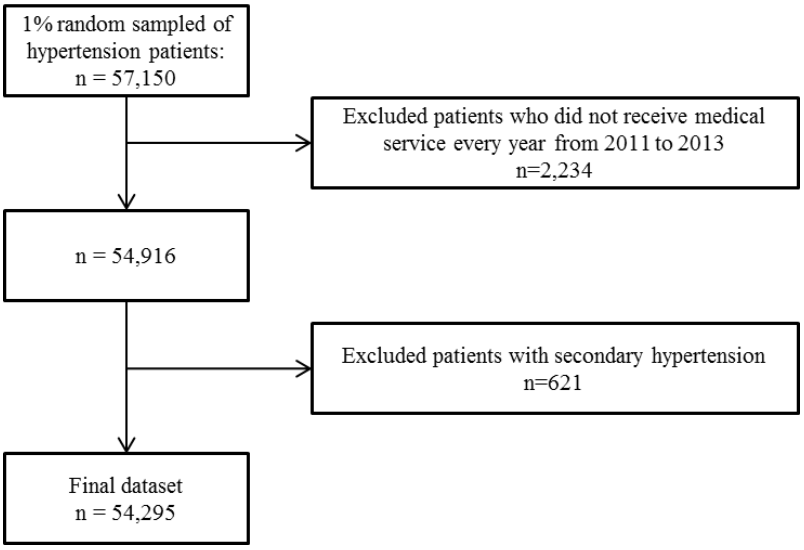


Figure 3. Selection of study population

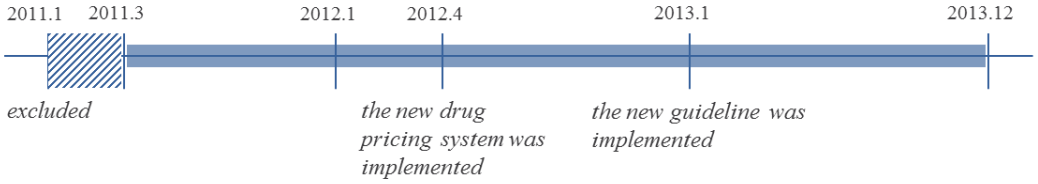


Figure 4. Study period for interrupted time series analysis

Dependent variables

Dependent variables were classified into two categories: utilization and expenditures. Data for all variables were collected monthly, so the unit of analysis was person-month.

For utilization, daily drug utilization, prescribing days, average number of drugs per month, percentage of original drugs per prescription, drug overutilization, and prohibited combinations were included in the analysis. Daily drug utilization represented how many subjects took antihypertensive agents per day. Daily dosage was adjusted by DDD. A daily drug utilization of one indicated that the daily dosage was equal to DDD. If daily drug utilization was over one, subjects took their drugs more than the DDD. The percentage of original drugs per prescription was calculated as (the number of original antihypertensive drugs / the number of all antihypertensive drugs) × 100. Prescribing more than two agents per ingredient is restricted by the new guideline. The drug overutilization and prohibited combinations variables were binary. The number of drug overutilization indicates how physicians violated the guideline by prescribing, for example, two beta blockers at one outpatient visit. The number of prohibited combination indicates physicians violated the prohibited combinations clause in the guideline, such as diuretic + alpha blocker.

Antihypertensive drug costs, antihypertensive drug cost per prescribing day, and outpatient medical costs were used. All costs were adjusted by hospital type and the annual growth rate of reimbursement based on 2013 data.[23] Total cost was examined as

the sum of antihypertensive drug costs and outpatient medical costs. An exchange rate of 1,000 KRW is 1 USD.

Independent variables

Age, sex, region, insurance type, Charlson comorbidity index (CCI), and combinations of antihypertensive agents were included as covariates. Age was classified into four groups, namely, under 49, 50–59, 60–69, over 70 years. Region was categorized into Seoul, metropolitan, and rural. There were two insurance types, namely, health insurance and medical aid. Medical aid is a type of health insurance for low-income people, like Medicaid in the US.[43] CCI was calculated yearly based on Quan's methods.[44] Nineteen diseases were classified into scores of 1, 2, 3, and 6 (Table 8)[45]. The CCI per subject was calculated from the sum of all scores. In this study, CCI was grouped as scores of 0, 1, 2, and over 3. Combinations of antihypertensive agents represented the number of kinds of antihypertensive agents that subjects took monthly. Combinations of antihypertensive agents are used to adjust the severity of the hypertension, for instance, in cases of resistant hypertension.[46] These were classified as 0, 1, 2, and over 3.

Table 8. Charlson comorbidity index scoring system

Score	Condition
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Moderate-to-severe renal failure
	Diabetes w/ end organ damage
	Any malignancy
	Leukemia / lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS/HIV

Source: Charlson et al.[45]

Statistical methods

Segmented regression analysis of interrupted time series analysis was used to assess policy effects. Our segmented regression analysis equation was in Equation 6:

$$Y_{it} = \beta_0 + \beta_1 \times time_t + \beta_2 \times new\ pricing\ system_t +$$
$$\beta_3 \times time\ after\ new\ pricing\ system_t + \beta_4 \times new\ guideline_t +$$
$$\beta_5 \times time\ after\ new\ guideline_t + \beta_6 \times season_t + X_{it} + e_{it} \cdots (6)$$

Y: dependent variables
i: each patient
t: time period
time: a continuous variable started in January 2011
new pricing system: a binary variable (0 before January 2012; 1 after April 2012)
time after new pricing system: a continuous variable started in April 2012
new guideline: a binary variable (0 before January 2013; 1 after February 2013)
time after new guideline: a continuous variable started in February 2013
season: seasonality (spring, summer, fall, winter)
X: independent variables
e: the error term

new guideline and *time after new guideline* were started in February 2013 because there was a 1-month lagged effect of the new guideline.

For this segmented regression analysis, each subject's data were aggregated monthly. To validate results, Generalized estimation equation (GEE) and a mixed model were conducted to compare results. *proc genmod* was used for GEE with *link identity*, *distribution normal*, and *AR(1)*. For the mixed model, *proc glimmix* was used with

random intercept, link identity, distribution normal, and *AR(1)*. SAS version 9.3 was used for all analyses. For binary variables, such as drug overutilization and prohibited combinations, a *probit* model was used in GEE. In this study, a subgroup analysis for insurance type was conducted.

As Medical aid beneficiaries' healthcare utilization behavior is different from health insurance subjects, it is needed to find out the policies' effects on Medical aid beneficiaries and health insurance beneficiaries.

Calculating marginal effects of policies

As the interpretation of segmented regression analysis is difficult because there are many variables related with time, marginal effects on dependent variables were calculated to display exact effects of policies. β_2 and β_3 were related to the new pricing policy. Marginal effects of only the new pricing policy in December 2012 compared to March 2012 can be calculated as $(\beta_2 + \beta_3 \times 9)$. Similarly, marginal effects of the new guideline in December 2013 compared to January 2013 can be calculated as $(\beta_4 + \beta_5 \times 11)$. The marginal effects of both policies in December 2013 compared to March 2012 is $(\beta_2 + \beta_3 \times 21 + \beta_4 + \beta_5 \times 11)$.

The coefficient estimates of drug overutilization and prohibited combinations were calculated in the *probit* model, as they were needed to transform to marginal effects at the sample means of variables for interpretation. They were calculated with the *margins* command in Stata 13. For example, they can be interpreted as increasing probability by amount of β_5 per unit increase.

V. Results

1. Results of decomposition analysis

Table 9 shows the distribution of antihypertensive drugs. Among 1230 total drugs, the prices of 671 drugs were reduced by the new pricing policy. All alpha blockers and Angiotensin-converting enzyme inhibitor(ACEI)++ diuretic agents were subject to the new pricing policy. All vasodilator agents, Cytidine 5'-diphosphocholine(CDP-choline), beta blocker + Calcium channel blocker(CCB) agents, ACEI + Calcium channel blocker(CCB) agents, and Angiotensin receptor blocker(ARB) + CCB agents were not reduced in price.

Table 9. The number of antihypertensive drugs by class, by price changed

(Unit: Number of drugs, %)

Antihypertensive drugs		Price reduced (N=671)	Not price-reduced (N=559)	Total (N=1,230)
Alpha blocker		20 (100.0)	0 (0.0)	20
Beta blocker		110 (71.4)	44 (28.6)	154
CCB		126 (46.2)	147 (53.8)	273
Diuretic		33 (68.8)	15 (31.3)	48
ARB		151 (56.1)	118 (43.9)	269
ACEI		60 (50.0)	60 (50.0)	120
Vasodilator		0 (0.0)	3 (100.0)	3
CDP-choline		0 (0.0)	1 (100.0)	1
Combinations	Beta blocker+Diuretic	24 (92.3)	2 (7.7)	26
	Beta blocker+CCB	0 (0.0)	1 (100.0)	1
	ARB+Diuretic	131 (47.0)	148 (53.0)	279
	ARB+CCB	0 (0.0)	18 (100.0)	18
	ACEI+Diuretic	14 (100.0)	0 (0.0)	14
	ACEI+CCB	1 (25.0)	3 (75.0)	4

ARB: Angiotensin receptor blocker
ACEI: Angiotensin-converting enzyme inhibitor
CCB: Calcium channel blocker
CDP-choline: Cytidine 5'-diphosphocholine

Table 10 shows the utilization of antihypertensive drugs from July 2011 to September

2013. Overall expenditures decreased steadily, changing from USD 9,419,122 before the new pricing system (July 2011 to March 2012) to USD 7,994,961 after the new guideline (January 2013 to September 2013). ARBs and CCBs each comprised over 20% of total pharmaceutical expenditures in all periods. The percentage of CCBs alone decreased from 29.23% before the new pricing system to 27.71% after the new guideline, but the use of combinations increased. The ARB + Diuretic and ARB + CCB combinations occupied 98% of the combination expenditures. The percentage of the ARB + Diuretic combination decreased slightly. It was 21.69% of total pharmaceutical expenditure before the new pricing system, and then it decreased by 1%. The percentage of the ARB + CCB combination had increased (July 2011 to March 2012: 21.69%; April 2012 to December 2012: 18.20%; January 2013 to September 2013: 20.35%). The percentage of beta blockers showed the largest reduction rate, as it changed from 8.95% before the new pricing system to 6.75% after the new guideline.

Table 10. Antihypertensive drug expenditures

(1,000 USD)

Antihypertensive drugs		Before the new pricing system 2011.7-2012.3		After the new pricing system and before the new guideline 2012.4-2012.12		After the new guideline 2013.1-2013.9	
		Expenditure	%	Expenditure	%	Expenditure	%
Alpha blocker		74.4	0.79	45.5	0.54	41.2	0.51
Beta blocker		843.3	8.95	603.3	7.10	539.8	6.75
CCB		2753.5	29.23	2350.7	27.67	2215.4	27.71
Diuretic		79.1	0.84	66.3	0.78	66.2	0.83
ARB		1923.7	20.42	1761.1	20.73	1616.8	20.22
ACEI		254.0	2.70	208.0	2.45	190.2	2.38
Vasodilator		1.0	0.01	0.9	0.01	0.8	0.01
CDP-choline		0.2	0.00	0.1	0.00	0.1	0.00
Combinations	Beta blocker+Diuretic	45.4	0.48	32.0	0.38	26.2	0.33
	Beta blocker+CCB	1.6	0.02	1.2	0.01	1.0	0.01
	ARB+Diuretic	2043.3	21.69	1856.7	21.85	1649.7	20.63
	ARB+CCB	1367.0	14.51	1546.6	18.20	1627.1	20.35
	ACEI+Diuretic	8.7	0.09	4.9	0.06	3.5	0.04
	ACEI+CCB	24.0	0.25	19.4	0.23	17.1	0.21
Total		9419.1	100.00	8496.7	100.00	7995.0	100.00

ARB: Angiotensin receptor blocker
ACEI: Angiotensin-converting enzyme inhibitor
CCB: Calcium channel blocker
CDP-choline: Cytidine 5'-diphosphocholine

The expenditure of 671 price-reduced drugs decreased over periods (July 2011 to March 2012: USD 4,527,163; April 2012 to December 2012: USD 3,376,635; January 2013.1 to September 2013: USD 3,138,736). However, the expenditures for 559 not price-reduced drugs increased with increasing quantities after the pricing policy reforms (July 2011 to March 2012: USD 4,891,958; April 2012.4 to December 2012: USD 5,120,094). The quantities of combinations related to ARB and ARB alone increased, but decreased to USD 4,856,226 after the guideline was adopted (Table 11).

The results of decomposition analysis for all antihypertensive drugs are presented in Tables 12 and 13. The pharmaceutical expenditures decreased by 9.8% after the pricing policy was implemented, and by 5.9% again after the guideline was adopted. There was almost no quantity change before and after the new pricing system. After the new pricing policies were implemented, the price index decreased. The quantity index and the price index decreased after the new guideline was implemented. Therapeutic choice indexes increased slightly following both policies.

The most noteworthy drug types were CCBs, ARBs, and their combinations, as they comprised the highest percentage of drug expenditures. The rate of decline in ARB and CCB expenditures were low. After the new drug pricing policy was implemented, the expenditure and quantity for the ARB + CCB combination increased and the ARB quantity index increased. The ARB therapeutic choice indexes increased in both periods.

Table 11. Expenditures on price-reduced and Not price reduced antihypertensive drugs

(1,000 USD)

Group	Antihypertensive drugs		Before the new pricing system 2011.7-2012.3		After the new pricing system and before the new guideline 2012.4-2012.12		After the new guideline 2013.1-2013.9	
			Expenditure	%	Expenditure	%	Expenditure	%
Price-reduced	Alpha blocker		74.4	0.79	45.5	0.54	41.2	0.44
	Beta blocker		748.8	7.95	517.9	6.10	458.8	4.87
	CCB		1557.3	16.53	1232.1	14.50	1169.8	12.42
	Diuretic		39.9	0.42	27.9	0.33	26.4	0.28
	ARB		989.1	10.50	749.6	8.82	694.6	7.37
	ACEI		163.6	1.74	132.8	1.56	124.0	1.32
	Vasodilator		0.0	-	0.0	-	0.0	-
	CDP-choline		0.0	-	0.0	-	0.0	-
	Combinations	Beta blocker+Diuretic	43.6	0.46	30.4	0.36	24.7	0.26
		Beta blocker+CCB	0.0	-	0.0	-	0.0	-
		ARB+Diuretic	901.7	9.57	635.4	7.48	595.9	6.33
		ARB+CCB	0.0	-	0.0	-	0.0	-
		ACEI+Diuretic	8.7	0.09	4.9	0.06	3.5	0.04
		ACEI+CCB	0.0	-	0.0	-	0.0	-
	Total		4527.2	100.00	3376.6	100.00	3138.7	100.00
Not price-reduced	Alpha blocker		0.0	-	0.0	-	0.0	-
	Beta blocker		94.6	1.00	85.4	1.01	81.0	0.95
	CCB		1196.2	12.70	1118.6	13.17	1045.6	12.31
	Diuretic		39.2	0.42	38.4	0.45	39.9	0.47
	ARB		934.6	9.92	1011.5	11.90	922.2	10.85
	ACEI		90.4	0.96	75.1	0.88	66.2	0.78
	Vasodilator		1.0	0.01	0.9	0.01	0.8	0.01
	CDP-choline		0.2	0.00	0.1	0.00	0.1	0.00
	Combinations	Beta blocker+Diuretic	1.7	0.02	1.5	0.02	1.5	0.02
		Beta blocker+CCB	1.6	0.02	1.2	0.01	1.0	0.01
		ARB+Diuretic	1141.6	12.12	1221.3	14.37	1053.8	12.40
		ARB+CCB	1367.0	14.51	1546.6	18.20	1627.1	19.15
		ACEI+Diuretic	0.0	-	0.0	-	0.0	-
		ACEI+CCB	24.0	0.25	19.4	0.23	17.1	0.20
	Total		4892.0	100.00	5120.0	100.00	4856.1	100.00

ARB: Angiotensin receptor blocker; ACEI: Angiotensin-converting enzyme inhibitor; CCB: Calcium channel blocker; CDP-choline: Cytidine 5'-diphosphocholine

Table 12. Results of the decomposition analysis for all antihypertensive drugs before and after the new pricing system

Antihypertensive drugs		Expenditure	Price	Quantity	Therapeutic choices
Alpha blocker		0.612	0.661	0.868	1.065
Beta blocker		0.715	0.732	1.004	0.974
CCB		0.854	0.895	0.949	1.006
Diuretic		0.838	0.832	0.981	1.027
ARB		0.915	0.892	1.034	0.992
ACEI		0.819	0.865	0.882	1.073
Vasodilator		0.919	0.968	1.179	0.806
CDP-choline		0.515	0.947	0.543	1.000
Combinations	Beta blocker+Diuretic	0.705	0.785	0.872	1.030
	Beta blocker+CCB	0.741	1.000	0.741	1.000
	ARB+Diuretic	0.909	0.847	1.006	1.067
	ARB+CCB	1.131	1.000	1.136	0.996
	ACEI+Diuretic	0.569	0.711	0.781	1.024
	ACEI+CCB	0.809	0.992	0.723	1.128
Total		0.902	0.881	0.990	1.034

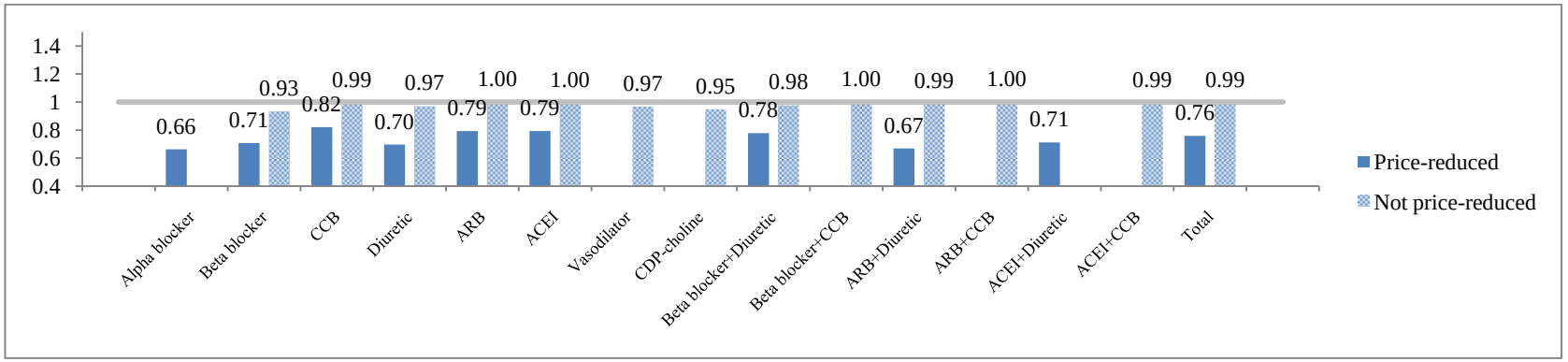
ARB: Angiotensin receptor blocker
ACEI: Angiotensin-converting enzyme inhibitor
CCB: Calcium channel blocker
CDP-choline: Cytidine 5'-diphosphocholine

Table 13. Results of the decomposition analysis for all antihypertensive drugs before and after the new guideline

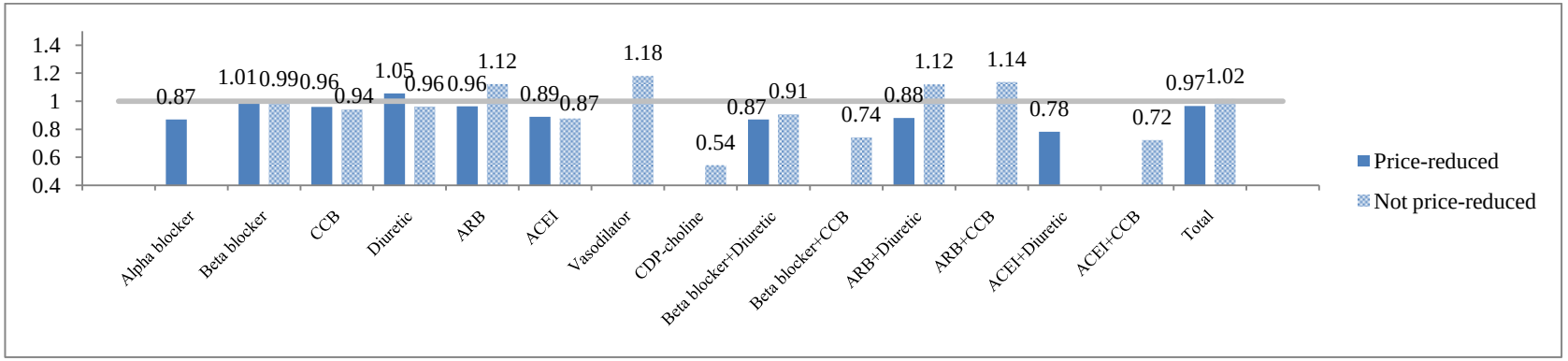
Antihypertensive drugs		Expenditure	Price	Quantity	Therapeutic choices
Alpha blocker		0.904	0.925	0.923	1.059
Beta blocker		0.895	0.943	0.972	0.977
CCB		0.942	0.984	0.945	1.014
Diuretic		0.999	0.957	0.979	1.066
ARB		0.918	0.932	0.989	0.996
ACEI		0.915	0.989	0.882	1.049
Vasodilator		0.867	0.958	0.912	0.991
CDP-choline		1.082	0.930	1.163	1.000
Combinations	Beta blocker+Diuretic	0.818	0.962	0.864	0.984
	Beta blocker+CCB	0.893	1.000	0.893	1.000
	ARB+Diuretic	0.889	0.928	0.959	0.999
	ARB+CCB	1.052	1.000	1.050	1.002
	ACEI+Diuretic	0.700	0.911	0.708	1.084
	ACEI+CCB	0.879	0.971	0.832	1.088
Total		0.941	0.960	0.967	1.013

ARB: Angiotensin receptor blocker
ACEI: Angiotensin-converting enzyme inhibitor
CCB: Calcium channel blocker
CDP-choline: Cytidine 5'-diphosphocholine

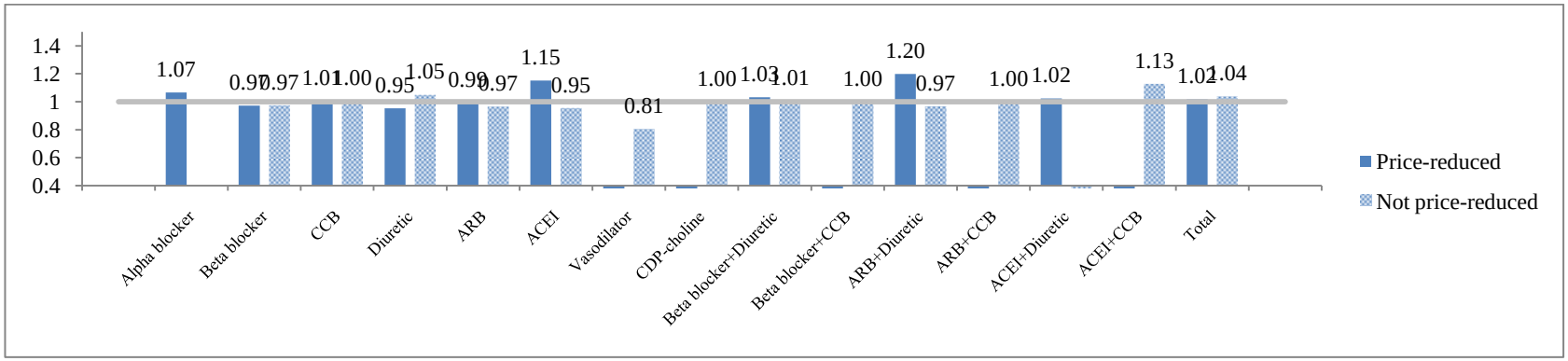
The results of the subgroup analysis for the adoption of the new pricing system are shown in Figure 6. After the new pricing policy was adopted, the quantity index of price-reduced drugs group decreased, but the quantity index of not price-reduced drugs increased. The therapeutic choice indexes increased in both groups. The expenditures for price-reduced drugs decreased by 25%, but the not price-reduced drug expenditures increased by 5%. The decreased expenditures for price-reduced drugs were caused by reductions in both quantity and price. After the new guideline was introduced, all indexes of the decomposition analysis changed similarly in both groups (Figure 7).



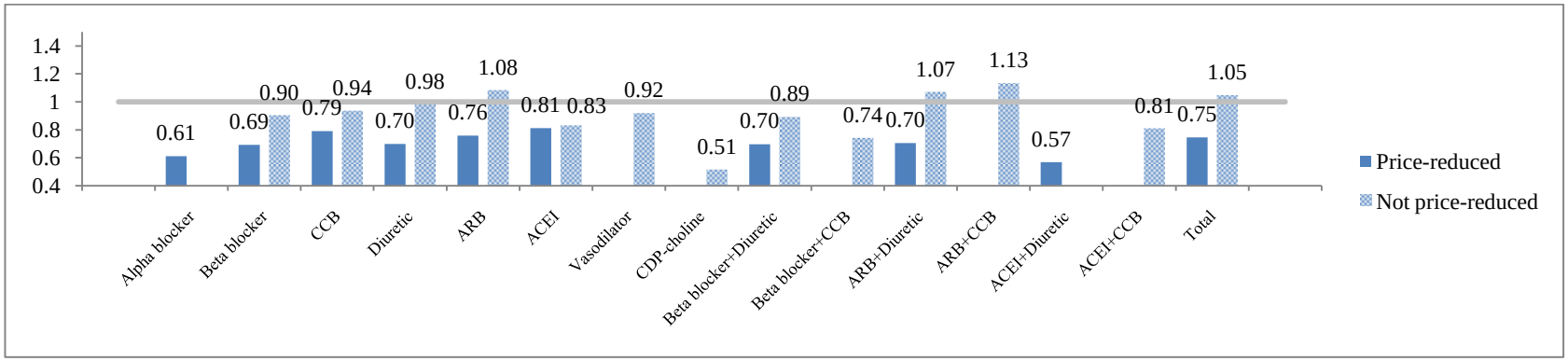
A. Price



B. Quantity



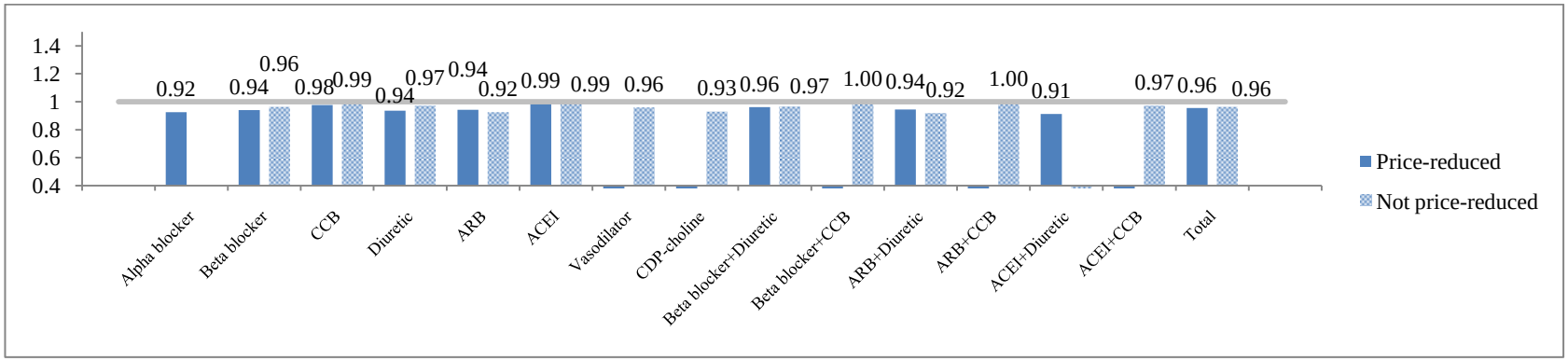
C. Therapeutic choice



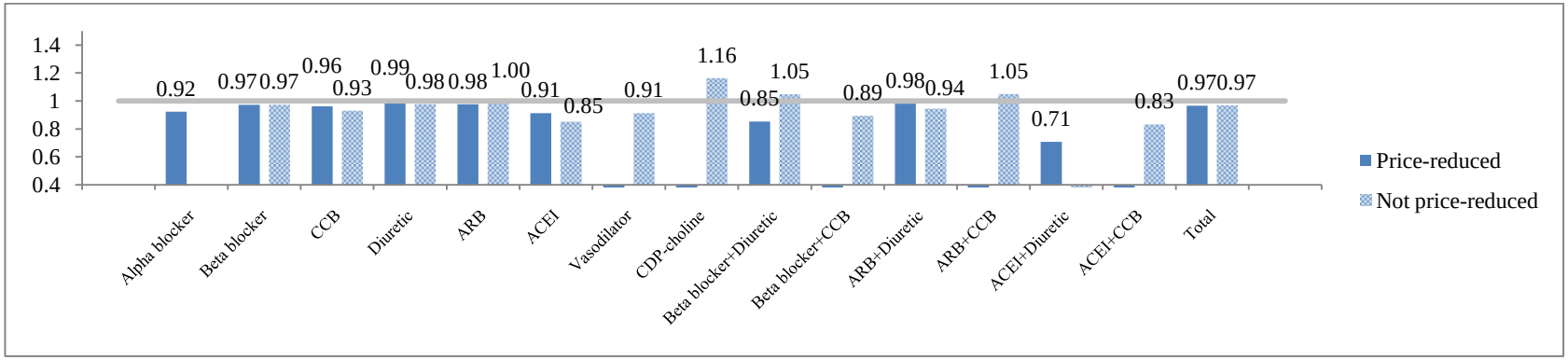
D. Expenditure

Figure 5. Results of decomposition analysis for the effects of the new pricing system between price-reduced and not price-reduced groups.

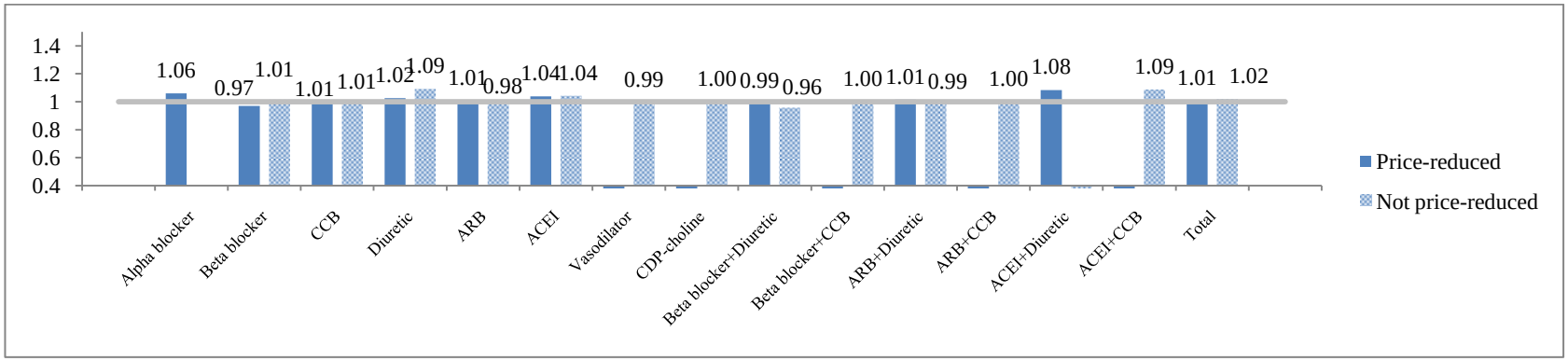
(ARB: Angiotensin receptor blocker; ACEI: Angiotensin-converting enzyme inhibitor; CCB: Calcium channel blocker; CDP-choline: Cytidine 5'-diphosphocholine)



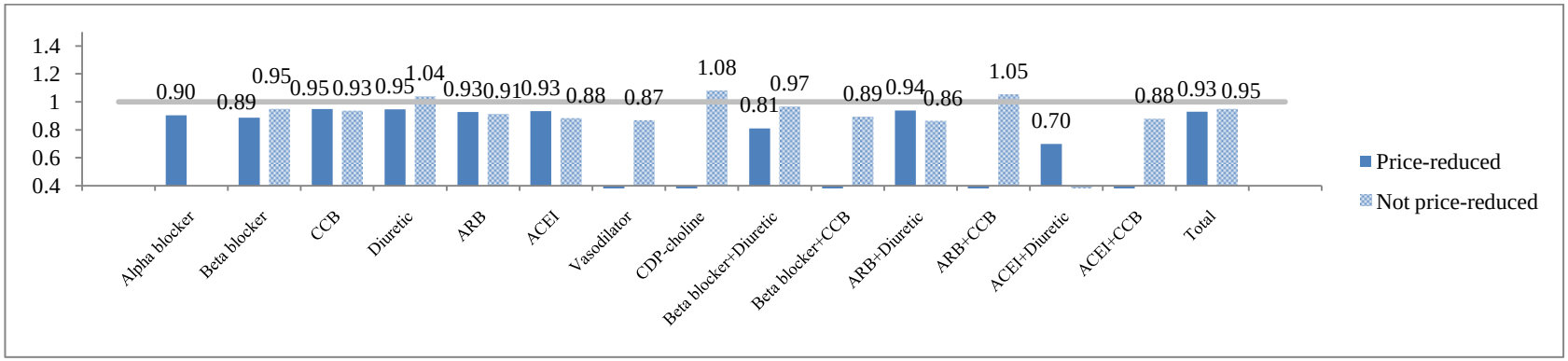
A. Price



B. Quantity



C. Therapeutic choice



D. Expenditure

Figure 6. Results of decomposition analysis for the effects of the new guideline between the price-reduced group and the not price-reduced group.

(ARB: Angiotensin receptor blocker; ACEI: Angiotensin-converting enzyme inhibitor; CCB: Calcium channel blocker; CDP-choline: Cytidine 5'-diphosphocholine)

2. Effects of policies with time trends

Study population

Table 14 shows the general subject characteristics in this study. A total of 54,295 subjects were included in our study. The highest proportion was in the over 70 years old group at 15,428. There were 24,842 (45.8%) men and 29,453 (54.3%) women. Most of the subjects had health insurance (93.8%). More than half lived in rural areas (53.6%). Combinations of hypertensive agents were scored as 0, 1, 2, and over 3, with 14,000 (6.2%), 14,571 (26.8%), 10,628 (19.6%), and 15,096 (27.8%) subjects, respectively.

Table 14. General characteristics of study subjects at baseline (Mar 2011)

		N	(%)
Age(y)	-49	8,982	16.5
	50-59	14,975	27.6
	60-69	14,910	27.5
	70-	15,428	28.4
Sex	Woman	29,453	54.3
	Man	24,842	45.8
Region	Seoul	11,831	21.8
	Metropolitan	13,356	24.6
	Rural	29,108	53.6
Insurance type	Health insurance	50,942	93.8
	Medical aid	3,353	6.2
Charlson comorbidity index	0	14,000	25.8
	1	14,571	26.8
	2	10,628	19.6
	3-	15,096	27.8
Combinations of hypertensive agents	0	3,295	6.1
	1	32,219	59.3
	2	14,183	26.1
	3-	4,598	8.5
Total		54,295	100.0

Trends of utilization and expenditures

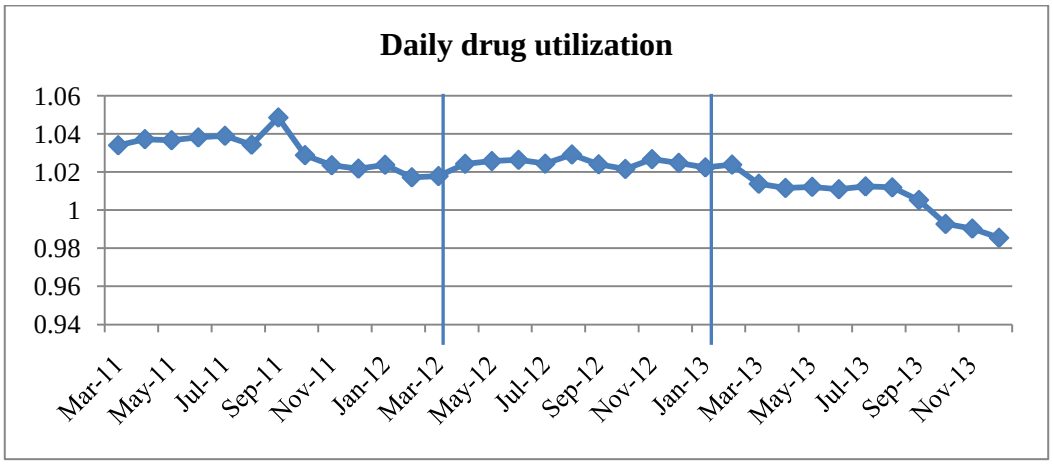
Table 15 shows the trends of each dependent variable for each year. Daily drug utilization was 0.99 before the new pricing system and 1.00 after the new pricing system was adopted. It decreased by 0.01 after the new guideline. Prescribing days per month increased after the new pricing system and decreased by 0.6 days after the new guideline was implemented. The percent of original drugs showed a declining trend. It was 60.5% from June 2011 to March 2012, 59.1% from April 2012 to January 2013, and 58.8% from February 2013 to September 2013. The number of drug overutilization, and the number of prohibited combinations decreased steadily.

Antihypertensive drug costs and antihypertensive drug cost per prescribing day decreased steadily. Antihypertensive drug cost per prescribing day decreased from USD 0.71 to USD 0.62. Outpatient medical costs increased after the new pricing policy and decreased after the new guideline. The sum of antihypertensive drug costs and outpatient medical costs decreased steadily. The monthly trends of dependent variables are displayed in Figure 8.

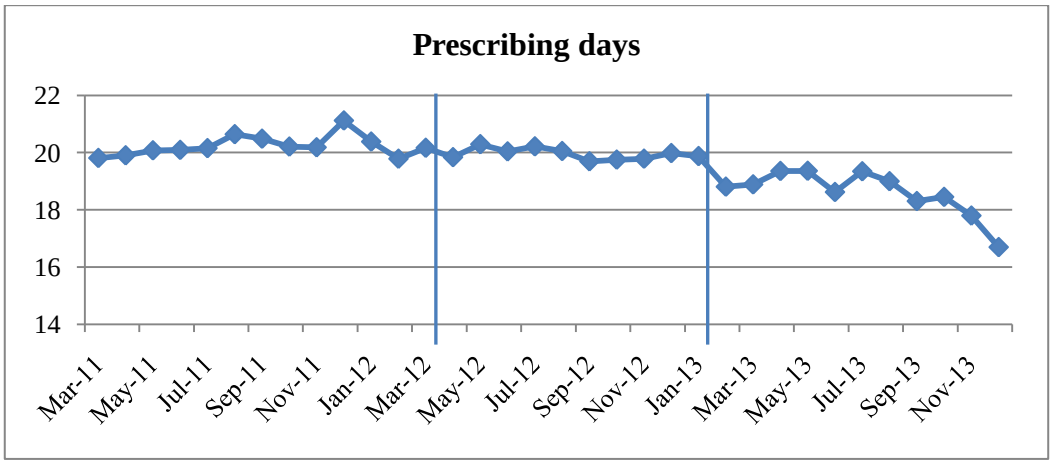
Table 15. Trends of utilization and expenditure by year

Unit: Mean±SD

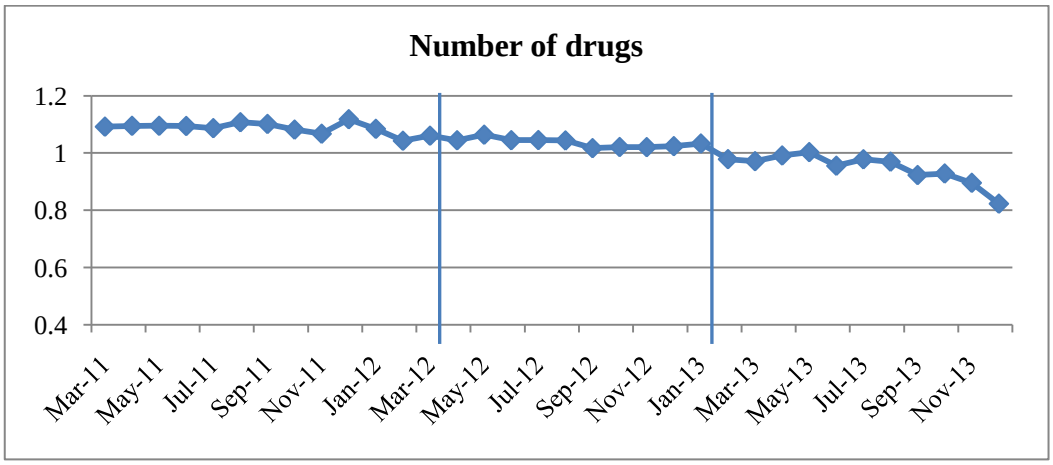
	Before the new pricing system 2011.6-2012.3	After the new pricing system and before the new guideline 2012.4-2013.1	After the new guideline 2013.2-2013.11	p-value
Daily drug utilization	0.99±0.57	1.00±0.49	0.97±0.50	<.001
Prescribing days per month(days)	22.0±9.87	23.9±9.08	23.3±9.23	<.001
Average number of drugs	1.36±0.73	1.35±0.69	1.31±0.69	<.001
Percent of original drugs (%)	60.5±42.3	59.1±42.9	58.8±43.4	<.001
Number of drug overutilization (n, %)	2478 (4.9)	1518 (3.3)	1391 (3.2)	<.001
Number of prohibited combinations (n, %)	5165 (10.3)	4584 (10.1)	4013 (9.2)	<.001
Antihypertensive drug costs (USD)	162.2±121.2	144.4±98.1	137.9±93.5	<.001
Antihypertensive drug cost per prescribing day (USD)	0.71±0.44	0.65±0.37	0.62±0.35	<.001
Outpatient medical costs (USD)	94.2±106.8	95.6±99.1	94.0±91.8	0.037
Outpatient medical costs + Antihypertensive drug costs (USD)	256.3±169.8	254.8±152.5	243.6±144.3	<.001



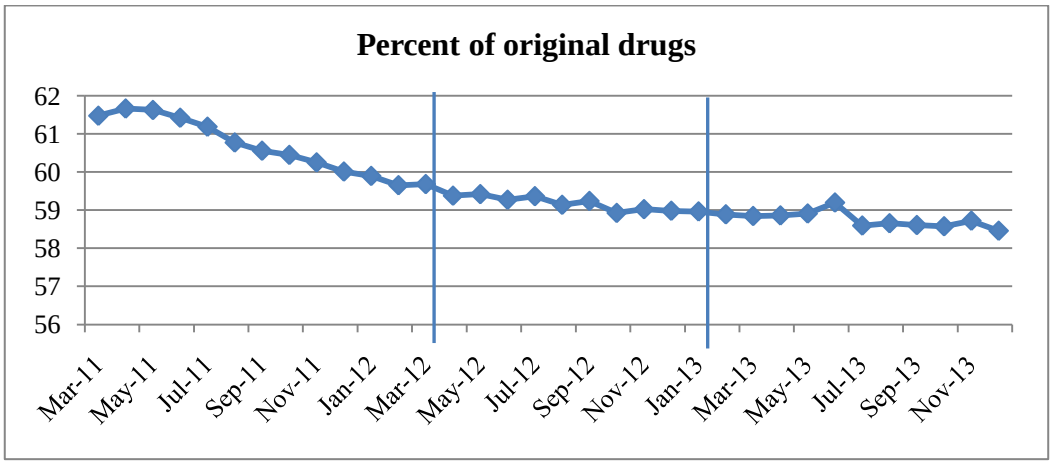
A. Daily drug utilization



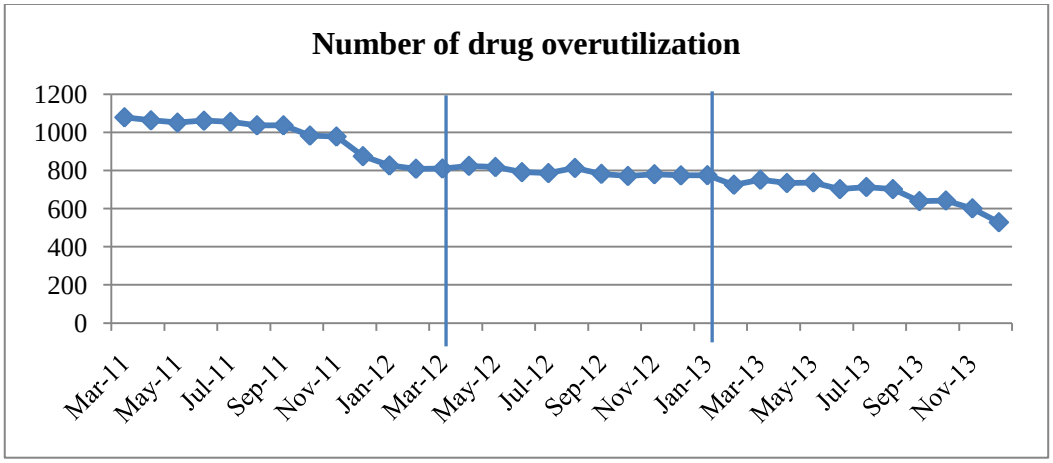
B. Prescribing days



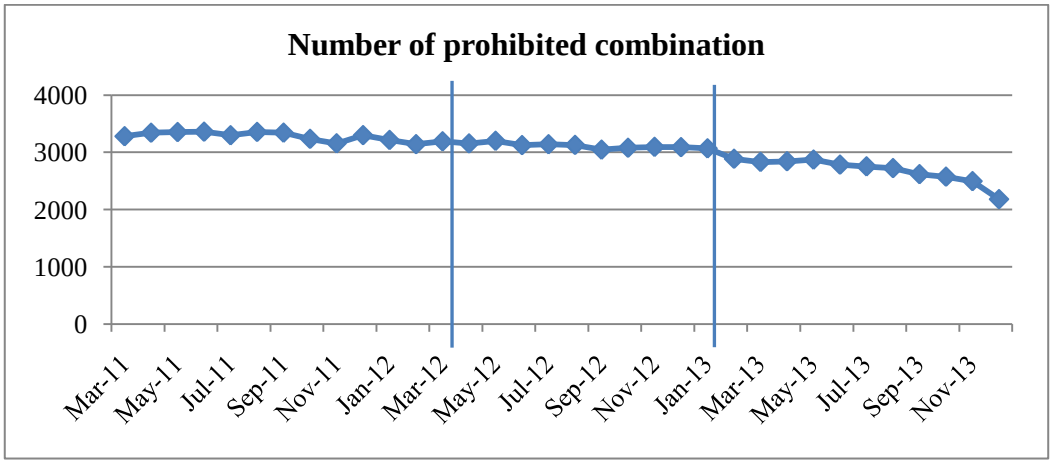
C. Number of drugs



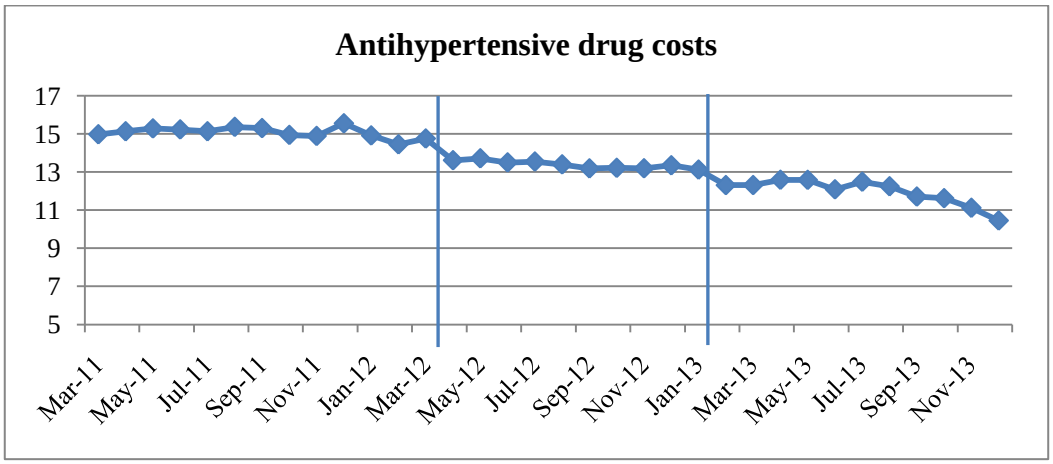
D. Percent of original drugs



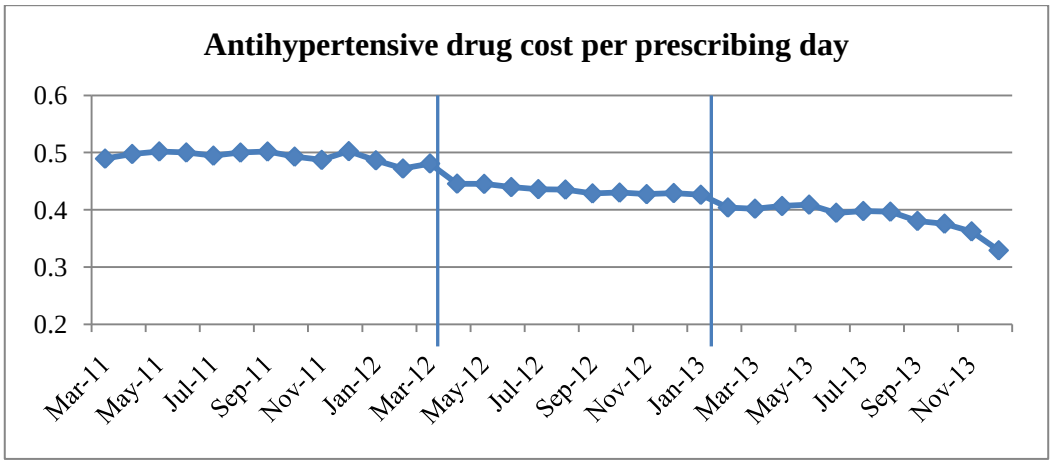
E. Number of drug overutilization



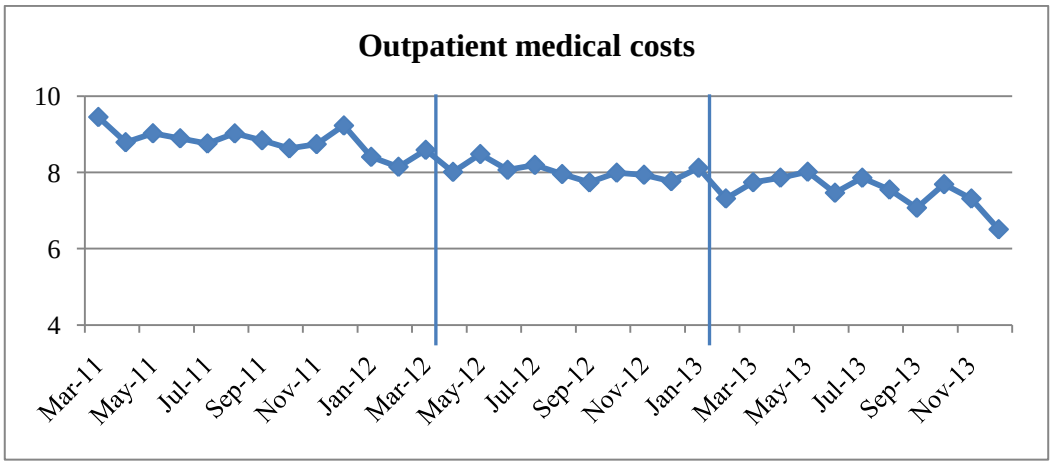
F. Number of prohibited combination



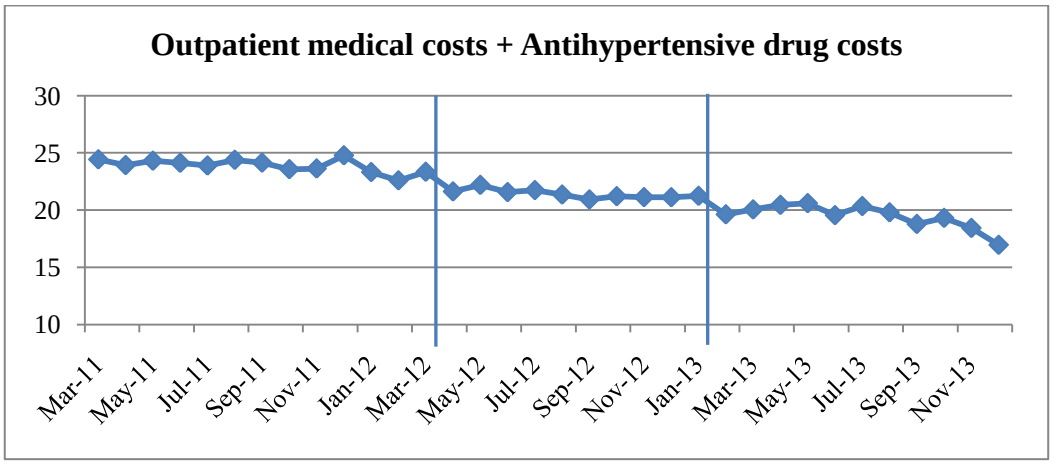
G. Antihypertensive drug costs



H. Antihypertensive drug cost per prescribing day



I. Outpatient medical costs



J. Outpatient medical costs + Antihypertensive drug costs

Figure 7. Trends of utilization, and expenditures per patient in Korea from Mar 2011 to Dec 2013

Results of segmented regression analysis

Table 16 and 17 show the results of the segmented regression analysis. The specific results including all estimates of covariates are attached as Appendix A.

There were differences between the GEE and mixed effects findings for the following variables: the results of time after the new pricing system for percent of original drugs, and the time after the new pricing system and new guideline for antihypertensive drug cost per prescribing day. These must be interpreted with caution.

Daily drug utilization increased significantly after the new pricing system (+0.0015; $p < 0.001$), and decreased after the guideline was implemented (-0.0038; $p < 0.001$). Prescribing days kept increasing over time, but decreased with the policy variable. Only the time variable was significant for percent of original drugs.

Antihypertensive drug cost per prescribing day decreased significantly by USD 0.0424 ($p < 0.001$) after the new drug pricing policy was implemented. The decrease after the new guideline was USD 0.0066 ($p < 0.001$). There was a significant downward trend (-0.074; $p<0.001$) after the new guideline. After the drug pricing system was implemented, antihypertensive drug cost (USD -1.3796; $p < 0.001$), outpatient medical costs (USD -0.7634; $p < 0.001$), and the sum of outpatient medical costs and antihypertensive drug costs (USD -2.2108; $p < 0.001$) changed significantly. After the new pricing system was implemented, outpatient medical costs, and sum of outpatient medical costs and antihypertensive drug costs rebounded. Expenditure variables showed a downward trend after the guideline was adopted.

The results of GEE probit for drug overutilization and prohibited combinations are presented in Table 17. Drug overutilization and prohibited combinations showed significant upward trends after the new pricing system was implemented. However, they changed to downward trends after the new guideline was implemented.

Table 16. Results of the segmented regression analysis for utilization and expenditure*

	Model	Time		New pricing system		Time after new pricing system		New guideline		Time after new guideline	
		Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
Daily drug utilization	*GEE*	**-0.0016**	**<.001**	0.0018	0.225	**0.0015**	**<.001**	**0.0035**	**0.026**	**-0.0038**	**<.001**
	Mixed	**-0.0012**	**<.001**	0.0014	0.584	**0.0010**	**0.002**	**0.0055**	**0.028**	**-0.0033**	**<.001**
Prescribing days (days)	*GEE*	**0.2453**	**<.001**	**-0.6401**	**<.001**	**-0.1060**	**<.001**	**-0.3721**	**<.001**	**-0.2650**	**<.001**
	Mixed	**0.1899**	**<.001**	**-0.7227**	**<.001**	**-0.0927**	**<.001**	**-0.2038**	**0.000**	**-0.2270**	**<.001**
Average number of drugs per month	*GEE*	**0.0047**	**<.001**	**-0.0265**	**<.001**	**0.0016**	**<.001**	**-0.0073**	**0.004**	**-0.0171**	**<.001**
	Mixed	**0.0041**	**<.001**	**-0.0336**	**<.001**	**-0.0007**	**0.029**	**0.0151**	**<.001**	**-0.0138**	**<.001**
Percent of original drugs (%)	*GEE*	**-0.0958**	**<.001**	-0.0457	0.557	0.0156	0.454	0.0460	0.535	0.0193	0.373
	Mixed	**-0.1226**	**<.001**	-0.0172	0.891	**0.0626**	**<.001**	-0.0788	0.531	0.0144	0.429
Antihypertensive drug costs (USD)	*GEE*	**0.0839**	**<.001**	**-1.3796**	**<.001**	**-0.0149**	**0.048**	**-0.3182**	**<.001**	**-0.2010**	**<.001**
	Mixed	**0.0665**	**<.001**	**-1.5210**	**<.001**	**-0.0279**	**<.001**	**-0.1026**	**0.031**	**-0.1724**	**<.001**
Antihypertensive drug cost per prescribing day (USD)	*GEE*	**0.0021**	**<.001**	**-0.0424**	**<.001**	-0.0002	0.443	**-0.0066**	**<.001**	**-0.0074**	**<.001**
	Mixed	**0.0018**	**<.001**	**-0.0488**	**<.001**	**-0.0011**	**<.001**	**0.0039**	**0.005**	**-0.0061**	**<.001**
Outpatient medical costs (USD)	*GEE*	0.0060	0.345	**-0.7634**	**<.001**	**0.0491**	**<.001**	**-0.3477**	**<.001**	**-0.0964**	**<.001**
	Mixed	0.0090	0.099	**-0.7059**	**<.001**	**0.0315**	**<.001**	**-0.2047**	**0.003**	**-0.0847**	**<.001**
Outpatient medical costs + Antihypertensive drug costs	*GEE*	**0.0987**	**<.001**	**-2.2136**	**<.001**	**0.0269**	**0.049**	**-0.6000**	**<.001**	**-0.2935**	**<.001**
	Mixed	**0.0799**	**<.001**	**-2.2257**	**<.001**	0.0021	0.853	**-0.3040**	**0.001**	**-0.2581**	**<.001**

*All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

Table 17. Results of the segmented regression analysis for drug over utilization and prohibited combination*

	Model	Time		New pricing system		Time after new pricing system		New guideline		Time after new guideline	
		Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value
Drug overutilization	*GEE Probit*	**-0.00033**	**<.001**	0.00025	0.383	**0.00037**	**<.001**	-0.00008	0.791	**-0.00022**	**0.016**
Prohibited combination	*GEE Probit*	**-0.00050**	**<.001**	-0.00019	0.692	**0.00088**	**<.001**	-0.00062	0.212	**-0.00073**	**<.001**

*All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

Marginal effects from segmented regression analysis results

Marginal effects for the dependent variables are presented in Table 18. Daily drug utilization significantly decreased by 0.0383 in December 2013 after implementation of the new guideline. Prescribing days decreased with both policies. For expenditures, antihypertensive drug costs decreased by USD 4.2217 in December 2013 with effects of both policies. These policies saved approximately 29.1% of antihypertensive drug costs from March 2012. Outpatient medical costs were reduced by approximately 13.6% from two policies in December 2013 compared to March 2013.

Table 18. Marginal effects from results of segmented regression analysis[†]

	Marginal effects		
	New pricing system in December 2012 (compared to March 2012)	New guideline in December 2013 (compared to January 2013)	Both policies in December 2013 (compared to March 2012)
Daily drug utilization	+0.0153	**-0.0383[‡]**	-0.0050
Prescribing days (days)	**-1.5941[‡]**	**-3.2871[‡]**	**-6.1532[‡]**
Average number of drugs per month	**-0.0121[‡]**	**-0.1954[‡]**	**-0.1883[‡]**
Percent of original drugs (%)	+0.0947	+0.2583	+0.5402
Antihypertensive drug costs (USD)	**-1.5137[‡]**	**-2.5292[‡]**	**-4.2217[‡]**
Antihypertensive drug cost per prescribing day (USD)	-0.0442	**-0.0880[‡]**	-0.1346
Outpatient medical costs (USD)	**-0.3215[‡]**	**-1.4081[‡]**	**-1.1404[‡]**
Outpatient medical costs + Antihypertensive drug costs	**-1.9715[‡]**	**-3.8285[‡]**	**-5.4772[‡]**
Drug overutilization (probability)	+0.00358	-0.00256	+0.00544
Prohibited combinations (probability)	+0.00768	-0.00867	+0.00952

[†]: All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

[‡]: variables related policies and times are significant ($p<0.05$)

Subgroup analysis

The results of the subgroup analysis for subjects with health insurance and medical aid are displayed in Tables 19–24. The specific results are attached as Appendices B and C. Their significances for subjects with health insurance were same as the results for all population except for daily drug utilization. However, the results for subjects with medical aid were different from the results for all population. Most effects of time after new pricing system were not significant; most effects of time after new guideline were significant.

Table 19. Results of the segmented regression analysis for utilization and expenditure for patients with health insurance*

	Model	Time		New pricing system		Time after new pricing system		New guideline		Time after new guideline	
		Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
Daily drug utilization	*GEE*	**-0.0016**	**<.001**	0.0022	0.143	**0.0015**	**<.001**	0.0027	0.104	**-0.0037**	**<.001**
	Mixed	**-0.0012**	**<.001**	0.0018	0.483	**0.0011**	**<.001**	0.0044	0.095	**-0.0032**	**<.001**
Prescribing days (days)	*GEE*	**0.2463**	**<.001**	**-0.6400**	**<.001**	**-0.1049**	**<.001**	**-0.4147**	**<.001**	**-0.2607**	**<.001**
	Mixed	**0.1909**	**<.001**	**-0.7221**	**<.001**	**-0.0912**	**<.001**	**-0.2436**	**<.001**	**-0.2246**	**<.001**
Average number of drugs per month	*GEE*	**0.0048**	**<.001**	**-0.0263**	**<.001**	**0.0016**	**<.001**	**-0.0100**	**<.001**	**-0.0169**	**<.001**
	Mixed	**0.0042**	**<.001**	**-0.0332**	**<.001**	-0.0007	0.055	**0.0127**	**<.001**	**-0.0137**	**<.001**
Percent of original drugs (%)	*GEE*	**-0.0971**	**<.001**	-0.0416	0.603	0.0211	0.322	0.0548	0.476	0.0064	0.774
	Mixed	**-0.1245**	**<.001**	-0.0050	0.969	**0.0700**	**<.001**	-0.1007	0.434	0.0055	0.769
Antihypertensive drug costs (USD)	*GEE*	**0.0858**	**<.001**	**-1.3828**	**<.001**	**-0.0164**	**0.033**	**-0.3524**	**<.001**	**-0.1956**	**<.001**
	Mixed	**0.0683**	**<.001**	**-1.5257**	**<.001**	**-0.0286**	**<.001**	**-0.1350**	**0.006**	**-0.1689**	**<.001**
Antihypertensive drug cost per prescribing day (USD)	*GEE*	**0.0022**	**<.001**	**-0.0423**	**<.001**	-0.0003	0.298	**-0.0074**	**<.001**	**-0.0073**	**<.001**
	Mixed	**0.0019**	**<.001**	**-0.0488**	**<.001**	**-0.0011**	**<.001**	**0.0032**	**0.026**	**-0.0060**	**<.001**
Outpatient medical costs (USD)	*GEE*	0.0085	0.180	**-0.7721**	**<.001**	**0.0462**	**<.001**	**-0.3570**	**<.001**	**-0.0954**	**<.001**
	Mixed	**0.0111**	**0.045**	**-0.7132**	**<.001**	**0.0283**	**0.001**	**-0.2119**	**0.002**	**-0.0835**	**<.001**
Outpatient medical costs + Antihypertensive drug costs	*GEE*	**0.1029**	**<.001**	**-2.2274**	**<.001**	0.0232	0.093	**-0.6476**	**<.001**	**-0.2877**	**<.001**
	Mixed	**0.0836**	**<.001**	**-2.2378**	**<.001**	-0.0017	0.886	**-0.3439**	**<.001**	**-0.2534**	**<.001**

*All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

Table 20. Results of the segmented regression analysis for drug overutilization and prohibited combination for patients with health insurance*

	Model	Time		New pricing system		Time after new pricing system		New guideline		Time after new guideline	
		Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value
Drug overutilization	*GEE Probit*	**-0.00032**	**<.001**	0.00035	0.236	**0.00035**	**<.001**	-0.00017	0.572	**-0.00021**	**0.025**
Prohibited combination	*GEE Probit*	**-0.00052**	**<.001**	-0.00027	0.596	**0.00088**	**<.001**	-0.00083	0.103	**-0.00069**	**<.001**

*All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

Table 21. Marginal effects from results of segmented regression analysis for patients with health insurance[†]

	Marginal effects		
	New pricing system in December 2012 (compared to March 2012)	New guideline in December 2013 (compared to January 2013)	Both policies in December 2013 (compared to March 2012)
Daily drug utilization	+0.0157	-0.0380	-0.0043
Prescribing days (days)	**-1.5841[‡]**	**-3.2824[‡]**	**-6.1252[‡]**
The average number of drugs per month	**-0.0119[‡]**	**-0.1959[‡]**	**-0.1886[‡]**
Percent of original drugs (%)	+0.1483	+0.1252	+0.5267
Antihypertensive drug costs (USD)	**-1.5304[‡]**	**-2.5040[‡]**	**-4.2312[‡]**
Antihypertensive drug cost per prescribing day (USD)	-0.0450	**-0.0877[‡]**	-0.1363
Outpatient medical costs (USD)	**-0.3563[‡]**	**-1.4064[‡]**	**-1.2083[‡]**
Outpatient medical costs + Antihypertensive drug costs	-2.0186	**-3.8123[‡]**	-5.5525
Drug overutilization (probability)	+0.00350	-0.00248	+0.00522
Prohibited combinations (probability)	+0.00765	-0.00842	+0.00979

[†]: All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

[‡]: variables related policies and times are significant ($p<0.05$)

Table 22. Results of the segmented regression analysis for utilization and expenditure for patients with medical aid

	Model	Time		New pricing system		Time after new pricing system		New guideline		Time after new guideline	
		Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
Daily drug utilization	*GEE*	-0.0014	0.147	-0.0040	0.628	0.0007	0.689	**0.0181**	**0.006**	**-0.0062**	**0.002**
	Mixed	-0.0004	0.590	-0.0079	0.340	-0.0009	0.356	**0.0263**	**0.002**	**-0.0045**	**<.001**
Prescribing days (days)	*GEE*	**0.2268**	**<.001**	**-0.6846**	**0.002**	**-0.1175**	**<.001**	0.3187	0.134	**-0.3373**	**<.001**
	Mixed	**0.1710**	**<.001**	**-0.7297**	**<.001**	**-0.1228**	**<.001**	0.4166	0.054	**-0.2687**	**<.001**
Average number of drugs per month	*GEE*	**0.0035**	**0.007**	**-0.0332**	**0.003**	0.0012	0.566	**0.0352**	**<.001**	**-0.0204**	**<.001**
	Mixed	**0.0031**	**<.001**	**-0.0393**	**<.001**	-0.0022	0.133	**0.0515**	**<.001**	**-0.0152**	**<.001**
Percent of original drugs (%)	*GEE*	-0.1001	0.098	-0.0657	0.849	-0.0470	0.637	-0.1195	0.679	0.1951	0.091
	Mixed	-0.1075	0.012	-0.1150	0.831	-0.0585	0.389	0.3751	0.490	**0.1839**	**0.021**
Antihypertensive drug costs (USD)	*GEE*	**0.0532**	**0.015**	**-1.3792**	**<.001**	0.0142	0.679	0.2265	0.199	**-0.2901**	**<.001**
	Mixed	**0.0407**	**0.009**	**-1.4454**	**<.001**	-0.0284	0.246	0.3763	0.051	**-0.2186**	**<.001**
Antihypertensive drug cost per prescribing day (USD)	*GEE*	0.0009	0.182	**-0.0453**	**<.001**	0.0011	0.318	0.0055	0.258	**-0.0094**	**<.001**
	Mixed	0.0008	0.078	**-0.0482**	**<.001**	-0.0007	0.351	**0.0138**	**0.016**	**-0.0067**	**<.001**
Outpatient medical costs (USD)	*GEE*	-0.0278	0.466	-0.6522	0.069	0.0899	0.084	-0.1436	0.667	**-0.1154**	**0.020**
	Mixed	-0.0239	0.392	-0.6077	0.084	0.0748	0.090	-0.0760	0.827	**-0.1064**	**0.032**
Outpatient medical costs + Antihypertensive drug costs	*GEE*	0.0388	0.424	**-2.082**	**<.001**	0.0869	0.212	0.1760	0.670	**-0.3918**	**<.001**
	Mixed	0.0225	0.521	**-2.056**	**<.001**	0.0456	0.411	0.3110	0.476	**-0.3275**	**<.001**

*All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

Table 23. Results of the segmented regression analysis for drug over utilization and prohibited combination for patients with medical aid

	Model	Time		New pricing system		Time after new pricing system		New guideline		Time after new guideline	
		Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value	Marginal effects	p-value
Drug overutilization	*GEE Probit*	-0.00125	0.093	-0.00183	0.648	0.00047	0.757	0.00353	0.433	-0.00279	0.151
Prohibited combination	*GEE Probit*	0.00117	0.241	**0.00987**	**0.020**	-0.00198	0.246	0.00500	0.254	-0.00128	0.500

*All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

Table 24. Marginal effects from results of segmented regression analysis for patients with medical aid[†]

	Marginal effects		
	New pricing system in December 2012 (compared to March 2012)	New guideline in December 2013 (compared to January 2013)	Both policies in December 2013 (compared to March 2012)
Daily drug utilization	+0.0023	**-0.0501[‡]**	-0.0394
Prescribing days (days)	**-1.7421[‡]**	-3.3916	-6.5437
Average number of drugs per month	-0.0224	**-0.1892[‡]**	-0.1972
Percent of original drugs (%)	-0.4887	+2.0266	+0.9739
Antihypertensive drug costs (USD)	-1.2514	-2.9646	-4.0456
Antihypertensive drug cost per prescribing day (USD)	-0.0354	-0.0979	-0.1201
Outpatient medical costs (USD)	+0.1569	-1.4130	-0.1773
Outpatient medical costs + Antihypertensive drug costs	-1.2999	-4.1338	-4.3909
Drug overutilization (probability)	+0.00240	-0.02716	-0.01912
Prohibited combinations (probability)	-0.00795	-0.00908	-0.04079

[†]: All results were adjusted by age, sex, region, insurance type, charlson comorbidity index, combinations of hypertension agents.

[‡]: variables related policies and times are significant ($p<0.05$)

VI. Discussion

1. Discussion of study methods

In this study, the effects of the new drug pricing system and the new guideline was identified by decomposition analysis and interrupted time series analysis. Decomposition analysis and interrupted time series analysis are popular methods for evaluating pharmaceutical policy.

Decomposition analysis is used by many researchers from a macro perspective to determine market size.[39,47] It is also used to identify factors associated with an increase in pharmaceutical expenditures.[5,15,36,48] Decomposition analysis is highly useful for identifying the rate of pharmaceutical expenditures in three aspects, namely, quantity, price, and therapeutic effect.[39] However, it is limited in that it is difficult to investigate the market entry of new drugs.[37] It is not an individual-level analysis, so the case-mix adjustment was not considered.[36]

There are two upgraded versions based on Gerdthan et al.[34], and Addis and Margrini's method.[37] Kwon and Yang[47] attached an additional part to the formula to determine the effect of newly reimbursed drugs. Wu et al.[48] investigated drug utilization for admission cases, and applied the equation to this problem. As this study did not consider inpatient cases, the effect of newly reimbursed drugs—a limitation of the data— Gerdthan et al.[34], Addis and Margrini's[37] decomposition was used in this study.

As drug reimbursement was connected with personal healthcare utilization data, segmented regression analysis of interrupted time series analysis is a useful method to evaluate policy evaluation.[41] It can compare the time series pattern before the intervention

with the pattern after the intervention. As systematic changes can occur over time, this analysis is frequently used to measure the degree of change in the use of medical care.[41,42,49-52]

Most studies using segmented analysis were analyzed with time-aggregated data without considering the personal level. Sen et al.'s study[42] used segmented regression analysis with data aggregated into "person-months." This study was conducted based on Sen et al.'s method, and thus it was able to overcome the limitation mentioned by most studies regarding an unadjusted case-mix.

This study employed the GEE model and mixed model. Model selection between GEE or mixed model is a matter of debate.[53] The strength of GEE is that it is a very flexible approach to analyze correlated data from the same subjects over time.[54,55] The limitation of the mixed model is the assumption of residual normality.[53,56] However, the GEE and mixed model are comparable for a continuous dependent variable.[57] Thus, the study results were interpreted based on the GEE, using the mixed model to check reliability. This is one reason for analyzing the drug overutilization and prohibited combinations variables with only the GEE.

2. Discussion of the results of decomposition analysis

In the results of decomposition analysis, Expenditures decreased, the price index decreased, the overall quantity index also decreased. However, the quantity index of not price-reduced drugs increased after the new pricing policy. Therapeutic choices increased.

The decomposition analysis indicated that most ARB related drugs quantity index increased or decreased very little. ARBs are more expensive than other types of antihypertensive drugs,[30] and physicians or pharmaceutical companies may continue to use ARB after the price cuts. Pharmaceutical companies might implement aggressive marketing strategies promoting expensive drugs or to increase drug quantities. Physicians often prescribe more drugs than a patient needs, or expensive drugs, because most drugs are covered by health insurance and there are no prescription limitations.[58]

The overall quantity index also decreased after the guideline wasss implemented, and the quantity of CCBs alone decreased, but the ARB + CCB combination increased, further evidencing an ARB preference phenomenon. The guideline did not restrict the use of expensive drugs. In USA, Medicare adopted a prior-authorization (PA) policy, which requests clinical information when physicians prescribe ARBs.[31,49] The purpose of the PA policy is to restrict the prescription rate for expensive drugs and to prevent pharmaceutical expenditures from increasing. As the purpose of the new guideline is to prevent increases in pharmaceutical expenditures, the Korean guideline should consider including this policy to manage the usage of expensive drugs with the cost-effectiveness analysis.

The usage of most ARB-related combinations increased following the enactment of both policies, which might represent an effect of recommendations of low doses and multiple antihypertensive combinations.[59,60] Prescribing low-dose antihypertensive drugs and

multiple combinations reduces side effects and shows increased efficacy compared to single doses of each individual agent.

There was concern about the deleterious health effects following guideline implementation.[61] Physicians usually prefer to prescribe multiple antihypertensive combinations, which can reduce per-drug dosages and side effects.[60] In the guideline, the ACEI + ARB combination was restricted. However, ACEI + ARB combination is effective on type 2 hypertensive microalbuminuric diabetic patients. Other restricted combinations are also effective for specific conditions,[62] and thus it is debatable whether these combinations should be restricted.

3. Discussion of the interrupted time series analysis results

Though the new guideline was adopted in January 2013, it was considered that the guideline actually changed physician behaviors in February 2013. The remarkable decreases between January and February 2013 are confirmed in Figure 8. For the segmented regression analysis, the time when the guideline was adopted was February 2013. This is different from the time when the guideline was adopted in the decomposition analysis. Thus, the additional decomposition analysis was conducted with a different time from when the guideline was adopted. The periods of the additional decomposition analysis were as follows: June 2011–March 2012, April 2012–January 2013, February 2013–November 2013. The results of this sensitivity analysis were almost identical to the existing results. The results are attached in Appendix C.

Generic drug utilization rates did not significantly change as a function of the policies. There are several reasons why the rate of generic drug utilization is low in Korea. Physicians usually prefer to prescribe original drugs,[16] even though all generics in Korea have passed bioequivalence tests, and the generic substitution of antihypertensive drugs does not lead to clinical problems.[18] Shin and Choi[63] reported non-price-based competition in South Korea, and so they suggested reducing generic drug prices. Because generic drug prices in South Korea are higher than in most other countries.[15] The reduction in drug prices may lead to the increased use of generic drugs. Godman et al.[27] evaluated the effects of policies to reduce reimbursement costs, and reported successful increases in generic drug utilization rates in Norway. Norway reduced the prices of only generics, and not originals. Creating a large price gap between generics and originals may be different from the new Korean pricing system.

The new pricing policy reduced patients' cost sharing.[24] Many countries increased cost sharing to prevent increasing pharmaceutical expenditures.[64,65] Goldman et al. reported that greater cost sharing is associated with reduced access.[65] It has been clearly identified among chronic disease patients, but the precise mechanisms are not clear. In this study, the daily drug utilization and the average number of drugs showed an upward trend after implementation of the new pricing system. In Korea, the selection and use of antihypertensive drugs is decided by physicians. Thus, it is not clear whether it was a balloon effect from reducing drug prices or the effects of the reduced cost sharing.

In the daily drug utilization results, the baseline time of the effect on daily drug utilization showed a decreasing trend. This may have been the effect of recommending low doses and multiple antihypertensive combinations.[59,60] However, daily drug utilization increased after the guideline was implemented. There were no dosage clauses in the guideline. There are only clauses for blood pressure condition and combinations. This might lead to an increase of quantity per day. However, it changed to a downward trend after the guideline.

Drug overutilization and prohibited combinations increased after the new pricing system and decreased after the new guideline. With increases in daily drug utilization, drug overutilization and prohibited combinations might increase. The guideline effectively reduced those cases.

The effect of the new guideline reduced expenditures more effectively than did the new drug pricing system in the segmented regression analysis. A substitution effect between drugs and outpatient utilization for price reduction was identified. From the perspective of Wettermark et al.,[21] the new pricing system may be considered the traditional model of regulatory strategies in pharmaceutical policy. On the contrary, the new guideline can be regarded as one mode of "soft regulations." Wettermark et al. mentioned that "soft

regulations" can be more effective than the traditional regulation model. Direct cost management policy, which is a kind of traditional regulation model, has difficulty controlling costs in empirical studies,[26,66] because companies have sought bypass strategies or increased the volume of sales.[67] Further research is necessary to identify the exact mechanism. The guideline was more effective in this study.

The health outcomes were not evaluated in this study. Kim et al.[11] reported that primary physicians' blood pressure control was poor in Korea. They mentioned that there are many patients who could benefit most from effective blood pressure control. In this situation, the guidelines might be effective for primary physicians.

4. Limitations

This study has the several limitations. Compliance to the guideline was not measured. For decomposition analysis, the case-mix was not adjusted because of the analysis is a macro perspective. For interrupted time series analysis, secondary hypertension patients were excluded from this study. Thus, these results do not represent all hypertension patients in Korea. As the unit of analysis was aggregated monthly per person, hospital characteristics were not captured in the analysis. It was adjusted for cost, but there may remain hospital effects in drug utilization variables.

VII. Conclusion

The policies saved money, but neither policy could control increasing the index of therapeutic choice. The pricing policy reform could not control total pharmaceutical expenditures of not price-reduced drugs, otherwise the prescription and reimbursement guideline reduced expenditures without increasing quantities. These policies could not control expensive drugs such as ARBs, CCBs, and combinations including ARBs, and they could not lead to the use of generic drugs. Even though they led to a decrease in total pharmaceutical expenditures, policymakers must consider the side effects and the comprehensive effects when implementing policies.

The guideline which is a kind of soft regulations was more effective, more reliable, less side effects than the direct cost control. The quantity index of not price-reduced drugs increased after the new pricing system was implemented, but they were controlled by the new guideline. The effect of the new guideline reduced expenditures more than the new drug pricing system in a segmented regression analysis. Further, the guideline worked to restrain improper prescriptions of antihypertensive drugs.

Future studies must focus not only on how policy can reduce expenditures, but also on whether less expensive drugs can be reasonably used as alternatives to their more expensive counterparts with considering health outcomes.

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Appendix

Appendix A. Detailed results of segmented regression analysis

Appendix A1. Result of segmented regression analysis for daily drug utilization

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	-0.0015	0.781	-0.0037	0.295
	60-69	-0.0055	0.322	-0.0024	0.568
	70-	-0.0024	0.687	-0.0048	0.292
Sex	Woman	.	.	.	.
	Man	-0.003	0.450	-0.0050	0.208
Region	Seoul	.	.	.	.
	Metropolitan	0.0028	0.613	0.0197	<.001
	Rural	0.0185	<.001	0.0241	<.001
Insurance type	Health insurance	.	.	.	.
	Medical aid	0.0147	0.079	0.0151	0.010
CCI	0	.	.	.	.
	1	-0.0076	0.017	-0.0091	<.001
	2	-0.0096	0.008	-0.0166	<.001
	3-	-0.0072	0.084	-0.0225	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	0.9383	<.001	0.6936	<.001
	2	0.9485	<.001	0.7263	<.001
	3	1.0034	<.001	0.7587	<.001
Season	Spring	.	.	.	.
	Summer	0.0024	0.006	0.0044	<.001
	Fall	0.0027	0.145	0.0025	0.067
	Winter	0.0025	0.041	0.0023	0.141
Time		-0.0016	<.001	-0.0012	<.001
New pricing policy		0.0018	0.225	0.0014	0.584
Time after new pricing policy		0.0015	<.001	0.0010	0.002
New guideline		0.0035	0.026	0.0055	0.028
Time after new guideline		-0.0038	<.001	-0.0033	<.001

Appendix A2. Result of segmented regression analysis for prescribing days

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	1.6763	<.001	1.4732	<.001
	60-69	2.0389	<.001	1.7674	<.001
	70-	1.4615	<.001	1.4464	<.001
Sex	Woman	.	.	.	.
	Man	-0.2691	<.001	-0.3392	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-0.8673	<.001	-0.4920	<.001
	Rural	-0.8848	<.001	-0.2267	<.001
Insurance type	Health insurance	.	.	.	.
	Medical aid	-1.3163	<.001	-1.0455	<.001
CCI	0	.	.	.	.
	1	-0.4601	<.001	-0.3156	<.001
	2	-1.0219	<.001	-0.7089	<.001
	3-	-2.5553	<.001	-1.6162	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	19.7506	<.001	13.2047	<.001
	2	26.0692	<.001	21.0998	<.001
	3	27.7059	<.001	24.5736	<.001
Season	Spring	.	.	.	.
	Summer	-0.1959	<.001	-0.0310	0.217
	Fall	-0.7304	<.001	-0.5826	<.001
	Winter	-0.6076	<.001	-0.4864	<.001
Time		0.2453	<.001	0.1899	<.001
New pricing policy		-0.6401	<.001	-0.7227	<.001
Time after new pricing policy		-0.1060	<.001	-0.0927	<.001
New guideline		-0.3721	<.001	-0.2038	<.001
Time after new guideline		-0.2650	<.001	-0.2270	<.001

Appendix A3. Result of segmented regression analysis for the average number of drugs per month

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.0820	<.001	0.0652	<.001
	60-69	0.1237	<.001	0.1023	<.001
	70-	0.1396	<.001	0.1221	<.001
Sex	Woman	.	.	.	.
	Man	0.0257	<.001	0.0273	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-0.0418	<.001	-0.0072	0.072
	Rural	-0.0260	<.001	0.0307	<.001
Insurance type	Health insurance	.	.	.	.
	Medical aid	-0.0441	<.001	-0.0190	0.001
CCI	0	.	.	.	.
	1	-0.0294	<.001	-0.0201	<.001
	2	-0.0529	<.001	-0.0352	<.001
	3-	-0.1024	<.001	-0.0716	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	0.7095	<.001	0.5513	<.001
	2	1.3062	<.001	1.1247	<.001
	3	2.0119	<.001	1.7681	<.001
Season	Spring	.	.	.	.
	Summer	-0.0057	<.001	-0.0004	0.749
	Fall	-0.0194	<.001	-0.0205	<.001
	Winter	-0.0264	<.001	-0.0233	<.001
Time		0.0047	<.001	0.0041	<.001
New pricing policy		-0.0265	<.001	-0.0336	<.001
Time after new pricing policy		0.0016	0.001	-0.0007	0.029
New guideline		-0.0073	0.004	0.0151	<.001
Time after new guideline		-0.0171	<.001	-0.0138	<.001

Appendix A4. Result of segmented regression analysis for percent of original drugs

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	-0.2636	0.344	1.3091	<.001
	60-69	-0.3672	0.252	1.5413	<.001
	70-	-0.8221	0.020	1.3184	<.001
Sex	Woman	.	.	.	.
	Man	1.9250	<.001	2.1797	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-1.3778	0.055	-1.2447	<.001
	Rural	-3.5378	<.001	-4.4596	<.001
Insurance type	Health insurance	.	.	.	.
	Medical aid	-0.4772	0.346	-1.2599	<.001
CCI	0	.	.	.	.
	1	-0.2735	0.011	-0.1256	0.109
	2	-0.1797	0.167	-0.0630	0.492
	3-	-0.3576	0.017	-0.2792	0.006
Combinations of hypertensive agents	0				
	1	.	.	.	.
	2	-0.1210	0.437	0.1696	0.048
	3	-0.7031	0.002	-1.9961	<.001
Season	Spring	.	.	.	.
	Summer	-0.0670	0.059	-0.0864	0.124
	Fall	-0.1154	0.008	-0.2118	0.002
	Winter	-0.0444	0.305	-0.0946	0.224
Time		-0.0958	<.001	-0.1226	<.001
New pricing policy		-0.0457	0.557	-0.0172	0.891
Time after new pricing policy		0.0156	0.454	0.0626	<.001
New guideline		0.0460	0.535	-0.0788	0.531
Time after new guideline		0.0193	0.373	0.0144	0.429

Appendix A5. Result of segmented regression analysis for antihypertensive drug cost

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.2334	0.018	0.3973	<.001
	60-69	-0.2084	0.041	0.1105	0.143
	70-	-1.2797	<.001	-0.4042	<.001
Sex	Woman	.	.	.	.
	Man	1.2981	<.001	1.4467	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-1.6716	<.001	-0.6957	<.001
	Rural	-1.5441	<.001	-0.4711	<.001
Insurance type	Health insurance	.	.	.	.
	Medical aid	-0.1693	0.181	0.1232	0.216
CCI	0	.	.	.	.
	1	-0.1928	0.002	-0.1240	<.001
	2	-0.2877	<.001	-0.2503	<.001
	3-	-0.6640	<.001	-0.6761	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	10.6087	<.001	7.7206	<.001
	2	19.0696	<.001	16.0404	<.001
	3	27.4072	<.001	23.8602	<.001
Season	Spring	.	.	.	.
	Summer	-0.1478	<.001	-0.0175	0.421
	Fall	-0.4553	<.001	-0.4093	<.001
	Winter	-0.3690	<.001	-0.3359	<.001
Time		0.0839	<.001	0.0665	<.001
New pricing policy		-1.3796	<.001	-1.5210	<.001
Time after new pricing policy		-0.0149	0.048	-0.0279	<.001
New guideline		-0.3182	<.001	-0.1026	0.031
Time after new guideline		-0.2010	<.001	-0.1724	<.001

Appendix A6. Result of segmented regression analysis for antihypertensive drug cost per prescribing days

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.0072	0.022	0.0106	<.001
	60-69	-0.0084	0.010	0.0024	0.292
	70-	-0.0417	<.001	-0.0121	<.001
Sex	Woman	.	.	.	.
	Man	0.0423	<.001	0.0479	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-0.0403	<.001	-0.0110	<.001
	Rural	-0.0351	<.001	-0.0007	0.681
Insurance type	Health insurance	.	.	.	.
	Medical aid	-0.0040	0.315	0.0048	0.112
CCI	0	.	.	.	.
	1	-0.0073	<.001	-0.0055	<.001
	2	-0.0111	<.001	-0.0106	<.001
	3-	-0.0247	<.001	-0.0255	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	0.3233	<.001	0.2521	<.001
	2	0.5944	<.001	0.5226	<.001
	3	0.8706	<.001	0.7851	<.001
Season	Spring	.	.	.	.
	Summer	-0.0035	<.001	-0.0010	0.110
	Fall	-0.0092	<.001	-0.0103	<.001
	Winter	-0.0116	<.001	-0.0114	<.001
Time		0.0021	<.001	0.0018	<.001
New pricing policy		-0.0424	<.001	-0.0488	<.001
Time after new pricing policy		-0.0002	0.443	-0.0011	<.001
New guideline		-0.0066	<.001	0.0039	0.005
Time after new guideline		-0.0074	<.001	-0.0061	<.001

Appendix A7. Result of segmented regression analysis for outpatient medical cost

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.4290	<.001	0.6138	<.001
	60-69	0.8760	<.001	1.1147	<.001
	70-	1.9774	<.001	2.1748	<.001
Sex	Woman	.	.	.	.
	Man	-0.4450	<.001	-0.4357	<.001
Region	Seoul	.	.	.	.
	Metropolitan	0.4564	<.001	0.3020	<.001
	Rural	1.7534	<.001	1.3424	<.001
Insurance type	Health insurance	.	.	.	.
	Medical aid	1.0531	<.001	0.8254	<.001
CCI	0	.	.	.	.
	1	0.4878	<.001	0.5738	<.001
	2	1.0587	<.001	1.0814	<.001
	3-	1.2609	<.001	1.4497	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	4.1270	<.001	4.3570	<.001
	2	7.8343	<.001	8.0717	<.001
	3	9.4771	<.001	10.1098	<.001
Season	Spring	.	.	.	.
	Summer	-0.2220	<.001	-0.1851	<.001
	Fall	-0.4461	<.001	-0.4029	<.001
	Winter	-0.5566	<.001	-0.4862	<.001
Time		0.0060	0.345	0.0090	0.099
New pricing policy		-0.7634	<.001	-0.7059	<.001
Time after new pricing policy		0.0491	<.001	0.0315	<.001
New guideline		-0.3477	<.001	-0.2047	0.003
Time after new guideline		-0.0964	<.001	-0.0847	<.001

Appendix A8. Result of segmented regression analysis for outpatient medical cost+antihypertensive drug cost

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.5819	<.001	0.9588	<.001
	60-69	0.6036	<.001	1.0779	<.001
	70-	0.6091	<.001	1.4324	<.001
Sex	Woman	.	.	.	.
	Man	0.8478	<.001	0.9459	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-1.2954	<.001	-0.6963	<.001
	Rural	0.0961	0.435	0.5199	<.001
Insurance type	Health insurance	.	.	.	.
	Medical aid	0.8749	<.001	0.7981	<.001
CCI	0	.	.	.	.
	1	0.3064	0.001	0.4400	<.001
	2	0.7901	<.001	0.8159	<.001
	3-	0.6406	<.001	0.7467	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	15.2109	<.001	12.4495	<.001
	2	27.5723	<.001	24.5997	<.001
	3	37.6997	<.001	34.5979	<.001
Season	Spring	.	.	.	.
	Summer	-0.3620	<.001	-0.2098	<.001
	Fall	-0.9560	<.001	-0.8266	<.001
	Winter	-0.9691	<.001	-0.8276	<.001
Time		0.0987	<.001	0.0799	<.001
New pricing policy		-2.2136	<.001	-2.2257	<.001
Time after new pricing policy		0.0269	0.049	0.0021	0.853
New guideline		-0.6000	<.001	-0.3040	0.001
Time after new guideline		-0.2935	<.001	-0.2581	<.001

Appendix A9. Result of segmented regression analysis for drug over utilization and prohibited combination

		Drug over utilization		Prohibited combination	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	-0.02659	0.193	-0.01381	0.284
	60-69	0.06410	0.002	-0.04718	0.001
	70-	0.17601	<.001	-0.05612	<.001
Sex	Woman	.	.	.	.
	Man	-0.03342	0.009	0.10663	<.001
Region	Seoul	.	.	.	.
	Metropolitan	0.04787	0.004	-0.10283	<.001
	Rural	0.07477	<.001	-0.07134	<.001
Insurance type	Health insurance	.	.	.	.
	Medical aid	0.13141	<.001	0.07976	<.001
CCI	0	.	.	.	.
	1	0.04431	<.001	0.02045	0.013
	2	0.10724	<.001	0.04427	<.001
	3-	0.19460	<.001	0.07937	<.001
Combinations of hypertensive agents	0				
	1	.	.	.	.
	2	0.96679	<.001	0.94913	<.001
	3	1.23860	<.001	1.52095	<.001
Season	Spring	.	.	.	.
	Summer	0.00467	0.374	-0.00047	0.878
	Fall	-0.00292	0.645	-0.01145	0.002
	Winter	-0.03680	<.001	-0.02869	<.001
Time		-0.01250	<.001	-0.00656	<.001
New pricing policy		0.00961	0.383	-0.00251	0.692
Time after new pricing policy		0.01396	<.001	0.01138	<.001
New guideline		-0.00305	0.791	-0.00806	0.212
Time after new guideline		-0.00853	0.015	-0.00952	<.001

Appendix B. Detailed results of segmented regression analysis for patients with health insurance

Appendix B1. Result of segmented regression analysis for drug utilization for patients with health insurance

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	-0.0014	0.799	-0.0034	0.349
	60-69	-0.0073	0.203	-0.0025	0.554
	70-	-0.0011	0.859	-0.0032	0.493
Sex	Woman	.	.	.	.
	Man	-0.0041	0.300	-0.0064	0.115
Region	Seoul	.	.	.	.
	Metropolitan	0.0016	0.782	0.0199	<.001
	Rural	0.0178	<.001	0.0247	<.001
CCI	0	.	.	.	.
	1	-0.0071	0.029	-0.0091	<.001
	2	-0.0106	0.005	-0.0181	<.001
	3-	-0.0062	0.147	-0.0228	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	0.9414	<.001	0.6912	<.001
	2	0.9505	<.001	0.7226	<.001
	3	1.0043	<.001	0.7514	<.001
Season	Spring	.	.	.	.
	Summer	0.0026	0.003	0.0046	<.001
	Fall	0.0032	0.107	0.0029	0.046
	Winter	0.0030	0.017	0.0025	0.118
Time		-0.0016	<.001	-0.0012	<.001
New pricing policy		0.0022	0.143	0.0018	0.483
Time after new pricing policy		0.0015	<.001	0.0011	0.001
New guideline		0.0027	0.104	0.0044	0.095
Time after new guideline		-0.0037	<.001	-0.0032	<.001

Appendix B2. Result of segmented regression analysis for prescribing days for patients with health insurance

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	1.6759	<.001	1.4605	<.001
	60-69	1.9933	<.001	1.7192	<.001
	70-	1.4190	<.001	1.4071	<.001
Sex	Woman	.	.	.	.
	Man	-0.2497	<.001	-0.3518	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-0.8566	<.001	-0.4674	<.001
	Rural	-0.8703	<.001	-0.2224	<.001
CCI	0	.	.	.	.
	1	-0.4409	<.001	-0.3018	<.001
	2	-1.0025	<.001	-0.6945	<.001
	3-	-2.5014	<.001	-1.5801	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	20.0002	<.001	13.3738	<.001
	2	26.1769	<.001	21.1427	<.001
	3	27.7621	<.001	24.5501	<.001
Season	Spring	.	.	.	.
	Summer	-0.1966	<.001	-0.0298	0.250
	Fall	-0.7398	<.001	-0.5875	<.001
	Winter	-0.6051	<.001	-0.4864	<.001
Time		0.2463	<.001	0.1909	<.001
New pricing policy		-0.6400	<.001	-0.7221	<.001
Time after new pricing policy		-0.1049	<.001	-0.0912	<.001
New guideline		-0.4147	<.001	-0.2436	<.001
Time after new guideline		-0.2607	<.001	-0.2246	<.001

Appendix B3. Result of segmented regression analysis for the average number of drugs per month for patients with health insurance

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.0812	<.001	0.0647	<.001
	60-69	0.1209	<.001	0.1005	<.001
	70-	0.1404	<.001	0.1232	<.001
Sex	Woman	.	.	.	.
	Man	0.0260	<.001	0.0265	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-0.0436	<.001	-0.0064	0.118
	Rural	-0.0263	<.001	0.0321	<.001
CCI	0	.	.	.	.
	1	-0.0283	<.001	-0.0201	<.001
	2	-0.0520	<.001	-0.0342	<.001
	3-	-0.1011	<.001	-0.0703	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	0.7173	<.001	0.5559	<.001
	2	1.3082	<.001	1.1215	<.001
	3	2.0093	<.001	1.7577	<.001
Season	Spring	.	.	.	.
	Summer	-0.0055	<.001	0.0002	0.880
	Fall	-0.0194	<.001	-0.0199	<.001
	Winter	-0.0262	<.001	-0.0230	<.001
Time		0.0048	<.001	0.0042	<.001
New pricing policy		-0.0263	<.001	-0.0332	<.001
Time after new pricing policy		0.0016	0.001	-0.0007	0.055
New guideline		-0.0100	<.001	0.0127	<.001
Time after new guideline		-0.0169	<.001	-0.0137	<.001

Appendix B4. Result of segmented regression analysis for percent of original drugs for patients with health insurance

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	-0.2317	0.419	1.3725	<.001
	60-69	-0.3482	0.289	1.5657	<.001
	70-	-0.7967	0.029	1.2611	<.001
Sex	Woman	.	.	.	.
	Man	1.7407	<.001	1.9864	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-1.2370	0.096	-0.9392	0.002
	Rural	-3.5719	<.001	-4.2537	<.001
CCI	0	.	.	.	.
	1	-0.3044	0.005	-0.1651	0.038
	2	-0.2248	0.093	-0.0900	0.335
	3-	-0.3831	0.012	-0.2613	0.011
Combinations of hypertensive agents	0				
	1	.	.	.	.
	2	-0.1439	0.372	0.1079	0.221
	3	-0.6548	0.007	-1.9821	<.001
Season	Spring	-0.0666	0.067	-0.0877	0.128
	Summer	-0.1058	0.017	-0.2010	0.004
	Fall	-0.0357	0.422	-0.0905	0.256
	Winter	-0.0971	<.001	-0.1245	<.001
Time		-0.0416	0.603	-0.0050	0.969
New pricing policy		0.0211	0.322	0.0699	<.001
Time after new pricing policy		0.0548	0.476	-0.1007	0.434
New guideline		0.0064	0.774	0.0055	0.769
Time after new guideline		0.0064	0.774	0.0055	0.769

Appendix B5. Result of segmented regression analysis for antihypertensive drug cost for patients with health insurance

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.1863	0.066	0.3556	<.001
	60-69	-0.3465	0.001	0.0238	0.758
	70-	-1.3619	<.001	-0.4652	<.001
Sex	Woman	.	.	.	.
	Man	1.3141	<.001	1.4390	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-1.6924	<.001	-0.6867	<.001
	Rural	-1.5486	<.001	-0.4456	<.001
CCI	0	.	.	.	.
	1	-0.1687	0.007	-0.1220	<.001
	2	-0.2582	<.001	-0.2241	<.001
	3-	-0.6283	<.001	-0.6544	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	10.7375	<.001	7.8294	<.001
	2	19.0976	<.001	16.0358	<.001
	3	27.2939	<.001	23.7234	<.001
Season	Spring	.	.	.	.
	Summer	-0.1477	<.001	-0.0155	0.490
	Fall	-0.4564	<.001	-0.4090	<.001
	Winter	-0.3668	<.001	-0.3351	<.001
Time		0.0858	<.001	0.0683	<.001
New pricing policy		-1.3828	<.001	-1.5257	<.001
Time after new pricing policy		-0.0164	0.033	-0.0286	<.001
New guideline		-0.3524	<.001	-0.1350	0.006
Time after new guideline		-0.1956	<.001	-0.1689	<.001

Appendix B6. Result of segmented regression analysis for antihypertensive drug cost per prescribing days for patients with health insurance

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.0056	0.082	0.0093	<.001
	60-69	-0.0126	<.001	0.0002	0.922
	70-	-0.0443	<.001	-0.0136	<.001
Sex	Woman	.	.	.	.
	Man	0.0428	<.001	0.0477	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-0.0409	<.001	-0.0105	<.001
	Rural	-0.0350	<.001	0.0004	0.817
CCI	0	.	.	.	.
	1	-0.0068	<.001	-0.0057	<.001
	2	-0.0104	<.001	-0.0098	<.001
	3-	-0.0238	<.001	-0.0251	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	0.3271	<.001	0.2554	<.001
	2	0.5954	<.001	0.5221	<.001
	3	0.8674	<.001	0.7802	<.001
Season	Spring	.	.	.	.
	Summer	-0.0035	<.001	-0.0008	0.210
	Fall	-0.0091	<.001	-0.0101	<.001
	Winter	-0.0114	<.001	-0.0113	<.001
Time		0.0022	<.001	0.0019	<.001
New pricing policy		-0.0423	<.001	-0.0488	<.001
Time after new pricing policy		-0.0003	0.298	-0.0011	<.001
New guideline		-0.0074	<.001	0.0032	0.026
Time after new guideline		-0.0073	<.001	-0.0060	<.001

Appendix B7. Result of segmented regression analysis for outpatient medical cost for patients with health insurance

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.4240	<.001	0.6525	<.001
	60-69	0.8631	<.001	1.1073	<.001
	70-	2.0607	<.001	2.2719	<.001
Sex	Woman	.	.	.	.
	Man	-0.4363	<.001	-0.4147	<.001
Region	Seoul	.	.	.	.
	Metropolitan	0.4722	<.001	0.3150	<.001
	Rural	1.7445	<.001	1.3385	<.001
CCI	0	.	.	.	.
	1	0.5020	<.001	0.5822	<.001
	2	1.0855	<.001	1.0856	<.001
	3-	1.2165	<.001	1.4487	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	3.8844	<.001	4.1628	<.001
	2	7.5362	<.001	7.7787	<.001
	3	9.0841	<.001	9.6996	<.001
Season	Spring	.	.	.	.
	Summer	-0.2300	<.001	-0.1917	<.001
	Fall	-0.4367	<.001	-0.3928	<.001
	Winter	-0.5477	<.001	-0.4747	<.001
Time		0.0085	0.180	0.0111	0.045
New pricing policy		-0.7721	<.001	-0.7132	<.001
Time after new pricing policy		0.0462	<.001	0.0283	0.001
New guideline		-0.3570	<.001	-0.2119	0.002
Time after new guideline		-0.0954	<.001	-0.0835	<.001

Appendix B8. Result of segmented regression analysis for outpatient medical cost+antihypertensive drug cost for patients with health insurance

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.5317	0.001	0.9541	<.001
	60-69	0.4549	0.006	0.9704	<.001
	70-	0.6109	<.001	1.4631	<.001
Sex	Woman	.	.	.	.
	Man	0.8736	<.001	0.9690	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-1.2998	<.001	-0.6732	<.001
	Rural	0.0806	0.523	0.5425	<.001
CCI	0	.	.	.	.
	1	0.3435	<.001	0.4524	<.001
	2	0.8485	<.001	0.8473	<.001
	3-	0.6351	<.001	0.7704	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	15.1040	<.001	12.3588	<.001
	2	27.3043	<.001	24.2935	<.001
	3	37.1824	<.001	34.0371	<.001
Season	Spring	.	.	.	.
	Summer	-0.3703	<.001	-0.2141	<.001
	Fall	-0.9487	<.001	-0.8158	<.001
	Winter	-0.9607	<.001	-0.8151	<.001
Time		0.1029	<.001	0.0836	<.001
New pricing policy		-2.2274	<.001	-2.2378	<.001
Time after new pricing policy		0.0232	0.093	-0.0017	0.886
New guideline		-0.6476	<.001	-0.3439	<.001
Time after new guideline		-0.2877	<.001	-0.2534	<.001

Appendix B9. Result of segmented regression analysis for drug over utilization and prohibited combination for patients with health insurance

		Drug over utilization		Prohibited combination	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	-0.03521	0.091	-0.02097	0.111
	60-69	0.04632	0.029	-0.05712	<.001
	70-	0.16969	<.001	-0.05435	<.001
Sex	Woman	.	.	.	.
	Man	-0.03204	0.016	0.09947	<.001
Region	Seoul				
	Metropolitan	0.05261	0.003	-0.10171	<.001
	Rural	0.07253	<.001	-0.06278	<.001
CCI	0	.	.	.	.
	1	0.04717	0.001	0.02431	0.004
	2	0.11009	<.001	0.04506	<.001
	3-	0.19811	<.001	0.08226	<.001
Combinations of hypertensive agents	0				
	1	.	.	.	.
	2	0.94371	<.001	0.93307	<.001
	3	1.22794	<.001	1.49331	<.001
Season	Spring	.	.	.	.
	Summer	0.00606	0.268	-0.00016	0.960
	Fall	-0.00052	0.938	-0.01132	0.003
	Winter	-0.33869	<.001	-0.02756	<.001
Time		-0.01221	<.001	-0.00676	<.001
New pricing policy		0.01359	0.236	-0.00344	0.596
Time after new pricing policy		0.01364	<.001	0.01143	<.001
New guideline		-0.00676	0.572	-0.01078	0.104
Time after new guideline		-0.00828	0.024	-0.00898	<.001

Appendix C. Detailed results of segmented regression analysis for patients with medical aid

Appendix C1. Result of segmented regression analysis for drug utilization for patients with medical aid

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	-0.0056	0.824	-0.0210	0.201
	60-69	0.0183	0.494	-0.0398	0.042
	70-	-0.0180	0.469	-0.0602	0.003
Sex	Woman	.	.	.	.
	Man	0.0193	0.275	0.0251	0.159
Region	Seoul	.	.	.	.
	Metropolitan	0.0188	0.455	0.0029	0.877
	Rural	0.0219	0.367	0.0058	0.722
CCI	0	.	.	.	.
	1	-0.0045	0.732	-0.0097	0.147
	2	-0.0040	0.762	0.0067	0.346
	3-	-0.0151	0.268	-0.0121	0.094
Combinations of hypertensive agents	0	.	.	.	.
	1	0.7918	<.001	0.7342	<.001
	2	0.8161	<.001	0.7889	<.001
	3	0.8723	<.001	0.8518	<.001
Season	Spring	.	.	.	.
	Summer	0.0002	0.948	-0.0005	0.891
	Fall	-0.0034	0.461	-0.0046	0.316
	Winter	-0.0067	0.145	-0.0031	0.553
Time		-0.0014	0.147	-0.0004	0.590
New pricing policy		-0.0040	0.628	-0.0079	0.340
Time after new pricing policy		0.0007	0.689	-0.0009	0.386
New guideline		0.0181	0.006	0.0263	0.002
Time after new guideline		-0.0062	0.002	-0.0045	<.001

Appendix C2. Result of segmented regression analysis for prescribing days for patients with medical aid

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	1.4632	<.001	1.7392	<.001
	60-69	3.0297	<.001	3.1291	<.001
	70-	2.3109	<.001	2.8960	<.001
Sex	Woman	.	.	.	.
	Man	-0.5008	0.022	-0.6024	0.014
Region	Seoul	.	.	.	.
	Metropolitan	-1.0351	0.001	-0.6560	0.027
	Rural	-1.1038	0.000	-0.3221	0.217
CCI	0	.	.	.	.
	1	-0.9063	0.002	-0.5813	0.001
	2	-1.3618	<.001	-0.9759	<.001
	3-	-3.1257	<.001	-2.0343	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	16.3648	<.001	10.9740	<.001
	2	24.8968	<.001	20.4493	<.001
	3	27.1732	<.001	24.7222	<.001
Season	Spring	.	.	.	.
	Summer	-0.1927	0.059	-0.0439	0.656
	Fall	-0.5819	<.001	-0.4947	<.001
	Winter	-0.6574	<.001	-0.4913	<.001
Time		0.2268	<.001	0.1710	<.001
New pricing policy		-0.6846	0.002	-0.7297	0.001
Time after new pricing policy		-0.1175	0.001	-0.1228	<.001
New guideline		0.3187	0.134	0.4166	0.054
Time after new guideline		-0.3373	<.001	-0.2687	<.001

Appendix C3. Result of segmented regression analysis for the average number of drugs per month for patients with medical aid

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.0917	<.001	0.0759	<.001
	60-69	0.1720	<.001	0.1429	<.001
	70-	0.1442	<.001	0.1317	<.001
Sex	Woman	.	.	.	.
	Man	0.0166	0.251	0.0182	0.221
Region	Seoul	.	.	.	.
	Metropolitan	-0.0119	0.567	-0.0086	0.617
	Rural	-0.0173	0.341	0.0089	0.557
CCI	0	.	.	.	.
	1	-0.0521	0.004	-0.0251	0.007
	2	-0.0678	<.001	-0.0502	<.001
	3-	-0.1181	<.001	-0.0859	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	0.6067	<.001	0.4798	<.001
	2	1.2929	<.001	1.1512	<.001
	3	2.0643	<.001	1.8769	<.001
Season	Spring	.	.	.	.
	Summer	-0.0103	0.061	-0.0091	0.083
	Fall	-0.0215	0.001	-0.0293	<.001
	Winter	-0.0313	<.001	-0.0282	<.001
Time		0.0035	0.007	0.0031	0.001
New pricing policy		-0.0332	0.003	-0.0393	0.001
Time after new pricing policy		0.0012	0.566	-0.0022	0.133
New guideline		0.0352	0.001	0.0515	<.001
Time after new guideline		-0.0204	<.001	-0.0152	<.001

Appendix C4. Result of segmented regression analysis for percent of original drugs for patients with medical aid

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	-0.5679	0.617	-0.5486	0.619
	60-69	0.8942	0.552	1.0722	0.440
	70-	1.2152	0.441	2.6903	0.068
Sex	Woman	.	.	.	.
	Man	3.5376	0.014	4.2607	0.004
Region	Seoul	0.0000	.	0.0000	.
	Metropolitan	-2.6980	0.316	-6.6838	<.001
	Rural	-1.7971	0.417	-7.7036	<.001
CCI	0				
	1	.	.	.	.
	2	1.1921	0.088	0.8980	0.047
	3-	1.5262	0.021	1.1687	0.015
Combinations of hypertensive agents	0	1.0837	0.156	0.0917	0.851
	1	.	.	.	.
	2	0.2741	0.647	1.0173	0.005
	3	-0.9290	0.243	-1.9231	0.001
Season	Spring	.	.	.	.
	Summer	-0.0387	0.804	-0.0295	0.903
	Fall	-0.2265	0.235	-0.3084	0.294
	Winter	-0.1789	0.333	-0.0735	0.826
Time		-0.1001	0.098	-0.1075	0.012
New pricing policy		-0.0657	0.849	-0.1150	0.831
Time after new pricing policy		-0.0470	0.637	-0.0585	0.389
New guideline		-0.1195	0.679	0.3751	0.490
Time after new guideline		0.1951	0.091	0.1839	0.021

Appendix C5. Result of segmented regression analysis for antihypertensive drug cost for patients with medical aid

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	1.1883	0.002	1.4271	<.001
	60-69	2.7531	<.001	2.2650	<.001
	70-	0.6633	0.041	1.3072	<.001
Sex	Woman	.	.	.	.
	Man	1.0133	<.001	1.2508	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-1.2409	0.002	-0.7320	0.015
	Rural	-1.3816	<.001	-0.9484	<.001
CCI	0	.	.	.	.
	1	-0.6077	0.055	-0.2175	0.164
	2	-0.6729	0.039	-0.6068	<.001
	3-	-0.9889	0.002	-0.8794	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	8.6981	<.001	6.2066	<.001
	2	18.6726	<.001	15.9446	<.001
	3	28.9538	<.001	25.3011	<.001
Season	Spring	.	.	.	.
	Summer	-0.1699	0.071	-0.0534	0.543
	Fall	-0.4442	<.001	-0.4242	<.001
	Winter	-0.3999	0.001	-0.3674	0.002
Time		0.0532	0.015	0.0407	0.009
New pricing policy		-1.3792	<.001	-1.4454	<.001
Time after new pricing policy		0.0142	0.679	-0.0284	0.246
New guideline		0.2265	0.199	0.3763	0.050
Time after new guideline		-0.2901	<.001	-0.2186	<.001

Appendix C6. Result of segmented regression analysis for antihypertensive drug cost per prescribing days for patients with medical aid

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.0402	0.002	0.0461	<.001
	60-69	0.0810	<.001	0.0575	<.001
	70-	0.0190	0.072	0.0329	0.004
Sex	Woman	.	.	.	.
	Man	0.0334	<.001	0.0409	<.001
Region	Seoul	.	.	.	.
	Metropolitan	-0.0276	0.026	-0.0166	0.074
	Rural	-0.0343	0.002	-0.0216	0.008
CCI	0	.	.	.	.
	1	-0.0130	0.172	-0.0044	0.349
	2	-0.0174	0.078	-0.0189	<.001
	3-	-0.0294	0.002	-0.0279	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	0.2683	<.001	0.2061	<.001
	2	0.5807	<.001	0.5235	<.001
	3	0.9140	<.001	0.8342	<.001
Season	Spring	.	.	.	.
	Summer	-0.0044	0.105	-0.0041	0.116
	Fall	-0.0107	0.001	-0.0142	<.001
	Winter	-0.0144	<.001	-0.0145	<.001
Time		0.0009	0.182	0.0008	0.078
New pricing policy		-0.0453	<.001	-0.0482	<.001
Time after new pricing policy		0.0011	0.318	-0.0007	0.351
New guideline		0.0055	0.258	0.0138	0.016
Time after new guideline		-0.0094	<.001	-0.0067	<.001

Appendix C7. Result of segmented regression analysis for outpatient medical cost for patients with medical aid

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.4848	0.416	-0.3328	0.524
	60-69	0.5798	0.319	0.9808	0.072
	70-	0.5164	0.330	0.5585	0.294
Sex	Woman	.	.	.	.
	Man	-0.7458	0.033	-0.4533	0.207
Region	Seoul	.	.	.	.
	Metropolitan	0.4106	0.292	0.3399	0.446
	Rural	2.0487	<.001	1.6735	<.001
CCI	0	.	.	.	.
	1	0.0966	0.826	0.4723	0.086
	2	0.4500	0.325	0.9583	0.001
	3-	1.4831	0.002	1.4784	<.001
Combinations of hypertensive agents	0	.	.	.	.
	1	6.9532	<.001	6.4136	<.001
	2	11.5016	<.001	11.2751	<.001
	3	14.2098	<.001	14.4024	<.001
Season	Spring	.	.	.	.
	Summer	-0.0903	0.566	-0.0764	0.629
	Fall	-0.5863	0.001	-0.5517	0.004
	Winter	-0.6780	0.001	-0.6659	0.002
Time		-0.0278	0.466	-0.0239	0.392
New pricing policy		-0.6522	0.069	-0.6077	0.084
Time after new pricing policy		0.0899	0.084	0.0748	0.090
New guideline		-0.1436	0.667	-0.0760	0.827
Time after new guideline		-0.1154	0.020	-0.1064	0.032

Appendix C8. Result of segmented regression analysis for outpatient medical cost+antihypertensive drug cost for patients with medical aid

		GEE		Mixed model	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	1.5287	0.045	1.0672	0.108
	60-69	3.2115	<.001	3.3771	<.001
	70-	1.0358	0.125	1.6466	0.015
Sex	Woman	.	.	.	.
	Man	0.2723	0.547	0.7137	0.121
Region	Seoul	.	.	.	.
	Metropolitan	-0.8870	0.122	-0.6141	0.280
	Rural	0.6265	0.238	0.5151	0.304
CCI	0	.	.	.	.
	1	-0.5080	0.359	0.2204	0.524
	2	-0.2718	0.636	0.3249	0.367
	3-	0.4817	0.405	0.5529	0.116
Combinations of hypertensive agents	0	.	.	.	.
	1	16.0279	<.001	13.0022	<.001
	2	30.8523	<.001	27.7775	<.001
	3	44.1421	<.001	40.5123	<.001
Season	Spring	.	.	.	.
	Summer	-0.2476	0.230	-0.1396	0.482
	Fall	-1.0811	<.001	-0.9962	<.001
	Winter	-1.1037	<.001	-1.0401	<.001
Time		0.0388	0.424	0.0225	0.521
New pricing policy		-2.0822	<.001	-2.0561	<.001
Time after new pricing policy		0.0869	0.212	0.0456	0.411
New guideline		0.1760	0.670	0.3107	0.476
Time after new guideline		-0.3918	<.001	-0.3275	<.001

Appendix C9. Result of segmented regression analysis for drug over utilization and prohibited combination for patients with medical aid

		Drug over utilization		Prohibited combination	
		Estimate	p-value	Estimate	p-value
Age(y)	-49	.	.	.	.
	50-59	0.03709	0.818	-0.05132	0.598
	60-69	-0.13939	0.430	-0.14354	0.215
	70-	-0.07679	0.660	-0.24881	0.039
Sex	Woman	.	.		.
	Man	-0.06662	0.594	0.36716	<.001
Region	Seoul	.	.	.	
	Metropolitan	0.01717	0.900	-0.17114	0.070
	Rural	0.11762	0.249	-0.03894	0.540
CCI	0	.	.	.	.
	1	-0.02542	0.733	-0.03262	0.445
	2	-0.00254	0.974	-0.04342	0.338
	3-	-0.03591	0.655	-0.01153	0.807
Combinations of hypertensive agents	0				
	1	.	.	.	.
	2	0.09103	0.144	0.00744	0.841
	3	0.13523	0.119	0.21368	<.001
Season	Spring	.	.	.	.
	Summer	0.01276	0.498	0.01177	0.268
	Fall	-0.01040	0.659	0.01121	0.387
	Winter	-0.03985	0.083	0.01617	0.196
Time		-0.01231	0.104	0.00607	0.233
New pricing policy		-0.01803	0.648	0.05125	0.020
Time after new pricing policy		0.00460	0.757	-0.01027	0.243
New guideline		0.03484	0.432	0.02594	0.253
Time after new guideline		-0.02753	0.143	-0.00664	0.498

Appendix D. Sensitivity analysis for decomposition

Appendix D1. Results of the decomposition analysis for all antihypertensive drugs before and after the new pricing system

Antihypertensive drugs		Expenditure	Price	Quantity	Therapeutic choices
Alpha blocker		0.607	0.656	0.865	1.070
Beta blocker		0.709	0.726	1.006	0.970
CCB		0.854	0.893	0.950	1.006
Diuretic		0.836	0.828	0.980	1.030
ARB		0.913	0.885	1.041	0.992
ACEI		0.812	0.862	0.878	1.074
Vasodilator		0.929	0.962	1.183	0.816
CDP-choline		0.500	0.940	0.530	1.003
Combinations	Beta blocker+Diuretic	0.695	0.782	0.864	1.029
	Beta blocker+CCB	0.747	1.000	0.747	1.000
	ARB+Diuretic	0.905	0.839	1.011	1.067
	ARB+CCB	1.153	1.000	1.158	0.996
	ACEI+Diuretic	0.545	0.709	0.737	1.043
	ACEI+CCB	0.788	0.992	0.705	1.127
Total		0.902	0.876	0.994	1.037

*from Jun 2011-Mar 2012 vs Apr 2012-Jan 2013

Appendix D2. Results of the decomposition analysis for all antihypertensive drugs before and after the new guideline

Antihypertensive drugs		Expenditure	Price	Quantity	Therapeutic choices
Alpha blocker		0.904	0.931	0.925	1.049
Beta blocker		0.884	0.947	0.956	0.976
CCB		0.924	0.985	0.924	1.015
Diuretic		0.986	0.961	0.964	1.065
ARB		0.899	0.926	0.978	0.993
ACEI		0.890	0.989	0.851	1.056
Vasodilator		0.858	0.962	0.843	1.058
CDP-choline		1.423	0.933	1.525	1.000
Combinations	Beta blocker+Diuretic	0.804	0.965	0.842	0.989
	Beta blocker+CCB	0.800	1.000	0.800	1.000
	ARB+Diuretic	0.867	0.923	0.940	0.999
	ARB+CCB	1.034	1.000	1.032	1.002
	ACEI+Diuretic	0.706	0.940	0.722	1.040
	ACEI+CCB	0.872	0.974	0.832	1.075
Total		0.923	0.959	0.949	1.014

*from Apr 2012-Jan 2013 vs Feb 2013-Nov 2013

Appendix D3. Results of the decomposition analysis for price-reduced antihypertensive drugs before and after the new pricing system

Antihypertensive drugs		Expenditure	Price	Quantity	Therapeutic choices
Alpha blocker		0.607	0.656	0.865	1.070
Beta blocker		0.686	0.701	1.011	0.968
CCB		0.790	0.817	0.960	1.008
Diuretic		0.693	0.693	1.052	0.951
ARB		0.752	0.783	0.965	0.996
ACEI		0.807	0.789	0.885	1.155
Vasodilator		-	-	-	-
CDP-choline		-	-	-	-
Combinations	Beta blocker+Diuretic	0.688	0.774	0.863	1.030
	Beta blocker+CCB	-	-	-	-
	ARB+Diuretic	0.699	0.661	0.881	1.200
	ARB+CCB	-	-	-	-
	ACEI+Diuretic	0.545	0.709	0.737	1.043
	ACEI+CCB	-	-	-	-
Total		0.742	0.754	0.968	1.017

*from Jun 2011-Mar 2012 vs Apr 2012-Jan 2013

Appendix D4. Results of the decomposition analysis for price-reduced antihypertensive drugs before and after the new guideline

Antihypertensive drugs		Expenditure	Price	Quantity	Therapeutic choices
Alpha blocker		0.904	0.931	0.925	1.049
Beta blocker		0.874	0.944	0.956	0.969
CCB		0.937	0.977	0.946	1.013
Diuretic		0.930	0.942	0.967	1.021
ARB		0.916	0.948	0.964	1.002
ACEI		0.913	0.987	0.886	1.044
Vasodilator		-	-	-	-
CDP-choline		-	-	-	-
Combinations	Beta blocker+Diuretic	0.795	0.965	0.829	0.993
	Beta blocker+CCB	-	-	-	-
	ARB+Diuretic	0.939	0.947	0.975	1.017
	ARB+CCB	-	-	-	-
	ACEI+Diuretic	0.706	0.940	0.722	1.040
	ACEI+CCB	-	-	-	-
Total		0.920	0.959	0.952	1.007

*from Apr 2012-Jan 2013 vs Feb 2013-Nov 2013

Appendix D5. Results of the decomposition analysis for not price-reduced antihypertensive drugs before and after the new pricing system

Antihypertensive drugs		Expenditure	Price	Quantity	Therapeutic choices
Alpha blocker		-	-	-	-
Beta blocker		0.896	0.929	0.990	0.975
CCB		0.936	0.991	0.941	1.003
Diuretic		0.983	0.967	0.961	1.058
ARB		1.086	0.993	1.135	0.963
ACEI		0.823	0.995	0.869	0.951
Vasodilator		0.929	0.962	1.183	0.816
CDP-choline		0.500	0.940	0.530	1.003
Combinations	Beta blocker+Diuretic	0.869	0.973	0.889	1.005
	Beta blocker+CCB	0.747	1.000	0.747	1.000
	ARB+Diuretic	1.068	0.979	1.129	0.966
	ARB+CCB	1.153	1.000	1.158	0.996
	ACEI+Diuretic	-	-	-	-
	ACEI+CCB	0.788	0.992	0.705	1.127
Total		1.052	0.990	1.020	1.042

*from Jun 2011-Mar 2012 vs Apr 2012-Jan 2013

Appendix D6. Results of the decomposition analysis for not price-reduced antihypertensive drugs before and after the new guideline

Antihypertensive drugs		Expenditure	Price	Quantity	Therapeutic choices
Alpha blocker		-	-	-	-
Beta blocker		0.941	0.966	0.955	1.020
CCB		0.910	0.994	0.903	1.014
Diuretic		1.027	0.975	0.963	1.095
ARB		0.887	0.910	0.992	0.983
ACEI		0.849	0.994	0.816	1.048
Vasodilator		0.858	0.962	0.843	1.058
CDP-choline		1.423	0.933	1.525	1.000
Combinations	Beta blocker+Diuretic	0.992	0.969	1.070	0.957
	Beta blocker+CCB	0.800	1.000	0.800	1.000
	ARB+Diuretic	0.829	0.910	0.916	0.995
	ARB+CCB	1.034	1.000	1.032	1.002
	ACEI+Diuretic	-	-	-	-
	ACEI+CCB	0.872	0.974	0.832	1.075
Total		0.924	0.958	0.946	1.019

*from Apr 2012-Jan 2013 vs Feb 2013-Nov 2013

Korean Abstract

약가 인하와 고혈압 약제 급여 및 처방 기준이 의료 사용행태와 지출에 미친 영향

서론: 현재 한국에서 약제비 지출의 증가는 해결해야할 주요 과제이다. 이에 한국 정부는 약제비 인하와 부적절한 처방을 줄이고자 2012년에 약가 산정 정책을 개편하고 약가인하를 하였고, 2013년에 고혈압 약제 처방 및 급여 기준을 신설하였다.

연구 목적: 이 연구의 목적은 약가 인하와 고혈압 약제 처방 및 급여 기준이 의료 사용행태와 지출에 어떠한 영향을 미쳤는지 알아보고자 하는 것이다.

연구 방법: Deterministic한 분석을 위해 Decomposition analysis을 사용하였고 stochastic 분석을 위해 interrupted time series analysis 분석 방법 중 segmented regression analysis 방법을 사용하였다. 자료는 심평원의 고혈압 환자표본자료를 사용하였고, segmented regression analysis에서 일차성 고혈압 54,295명을 연구 대상으로 포함하였다. 연구 기간은 2011년 3월부터 2013년 12월까지이다. 사용한 종속 변수는 항고혈압 의약품 사용행태로써 일일 약품 사용량, 처방일수, 월 평균 복용 약품목수, 오리지널 약제 처방률, 동종 성분 과다처방, 금지 병용 요법 처방을 포함하였다. 의료비 지출에 관한 변수로 월 평균 항고혈압약 약제비, 처방일당 항고혈압약 약제비, 고혈압으로 방문한 외래의 진료비를 포함하였다.

연구 결과: Decomposition analysis 분석 결과 약제비 지출은 약가 인하 후 9.8%감소하였고, 그 이후 처방·급여 기준 도입 후 5.9% 감소하였다. 약가 인하 후 약가 인하에 적용된 약제들의 사용량(-3%)과 지출(-25%)는 감소하였으나 약가 인하에 적용되지 않은 약제들의 사용량(2%)과 지출(5%)은 증가하였다. 처방·급여 기준이 도입된 이후에는 약가 인하 적용 약제군(-7%), 약가 인하 미적용 약제(-5%) 모두 약제비 지출이 감소하였다. Therapeutic choice index는 두 정책에서 모든 군에서 증가하였다. 처방·급여 기준은 수량 증가 없이 약제비 증가를 감소시켰다. 하지만 이들 정책들은 angiotensin receptor blockers나 calcium channel blockers와 같은 비싼 약제들의 사용 증가를 통제하지 못하였다.

Segmented regression analysis 분석 결과 2012년 3월과 비교했을 때 2013년 12월에는 항고혈압약 약제비와 외래 진료비가 약 USD 5.47 (29.1%)가 감소하였고, 항고혈압약 약제비는 USD 4.22 (28%) 감소하였다. 처방·급여 기준으로 인한 의료비 감소효과가 약가인하로 인한 의료비 감소효과보다 더 컸다. 오리지널 약품 이용률은 정책과 관련하여 유의한 변화가 없었다. 약가 인하 후 처방·급여 기준에 명시되어 있는 동종성분 과다처방 및 금지 병용 처방이 증가하였으나 처방·급여 기준 도입 후 감소하였다.

결론: 정책 수립시 각 정책이 어떠한 방식으로 영향을 끼칠 것인지를 고려할 필요가 있다. 약가 인하와 처방·급여 기준 도입에 따라 의료비가 절감되었으나 약가 인하에 따른 몇몇 부작용이 있었다. 처방·급여 기준과 같은 Soft regulations과 같은 가이드라인으로 규제를 하는 것이 직접적인 가격 통제보다 효과가 좋고 부작용도 적었기 때문에 좀 더 안정적인 정책이라 할 수 있다.

핵심어: 항고혈압 약제, 약가 인하, 처방·급여 기준, 의약품 사용 행태, 의료비 지출