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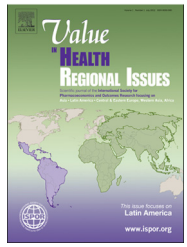

Prediction of Change in Prescription Ingredient Costs and Co-payment Rates under a Reference Pricing System in South Korea

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ABSTRACT

Background: The reference pricing system (RPS) establishes reference prices within interchangeable reference groupings. For drugs priced higher than the reference point, patients pay the difference between the reference price and the total price. **Objectives:** To predict potential changes in prescription ingredient costs and co-payment rates after implementation of an RPS in South Korea. **Methods:** Korean National Health Insurance claims data were used as a baseline to develop possible RPS models. Five components of a potential RPS policy were varied: reference groupings, reference pricing methods, co-pay reduction programs, manufacturer price reductions, and increased drug substitutions. The potential changes for prescription ingredient costs and co-payment rates were predicted for the various scenarios. **Results:** It was predicted that transferring the difference (total price minus reference price) from the insurer to patients would reduce ingredient costs from 1.4% to 22.8% for the third-party payer (government), but patient co-payment rates would increase from a baseline of 20.4% to 22.0% using chemical groupings and to 25.0% using therapeutic groupings. Savings rates in prescription ingredient costs (government and patient combined) were predicted to range from 1.6% to 13.7% depending on various scenarios. Although the co-payment rate would increase, a 15% price reduction by manufacturers coupled with a substitution rate of 30% would result in a decrease in the co-payment amount (change in absolute dollars vs. change in rates). **Conclusions:** Our models predicted that the implementation of RPS in South Korea would lead to savings in ingredient costs for the third-party payer and co-payments for patients with potential scenarios.

Keywords: co-payment, cost-containment, reference pricing system, South Korea.

Introduction

The South Korean National Health Insurance (NHI) system is managed by the government as a single payer and covers virtually all of its citizens, spending more than 7% of its gross domestic product on health care [1,2]. Pharmaceutical spending in South Korea was estimated at 20.6% of total health expenditures in 2013 and was much higher than the average (16.6%) estimated by the Organisation for Economic Cooperation and Development for 36 developed nations [3]. In South Korea, prescription drug expenditures paid by the NHI have increased about 13.2% annually from 2001 to 2010 [4]. The Korean government has adopted several drug pricing policies in an attempt to slow the growth of spending on prescriptions. In 2006, the government introduced the Drug Expenditure Rationalization Plan, which established a positive list system and price negotiations between the National Health Insurance Corporation (NHIC) and pharmaceutical manufacturers [5]. The Drug Reimbursement Examination Committee of the Health Insurance Review and Assessment Service (HIRA) determines reimbursement eligibility for new drugs on the basis of clinical usefulness, cost-effectiveness, budget impact, present status of reimbursement, and prices in other countries [6,7]. As part of this pricing reform, the Korean government has also re-evaluated drugs that had been previously listed, in some cases reducing the reimbursement amount or withdrawing the drug from the list of insured products [4,8]. In 2012, according to a new pricing system using the principle that the same active ingredients should have the same prices, the price of listed drugs decreased by 14.2% on average [1]. Despite these reforms, pharmaceutical expenditures have continued to rise 2.5% annually from 2010 to 2013 [9,10]. Patients have shown a preference for branded or high-priced generic medications even though their co-pay on lower priced generics is reduced [11,12]. Previous pricing policies have targeted manufacturers to reduce prices; it is, however, necessary to also address behaviors of patients, physicians, and

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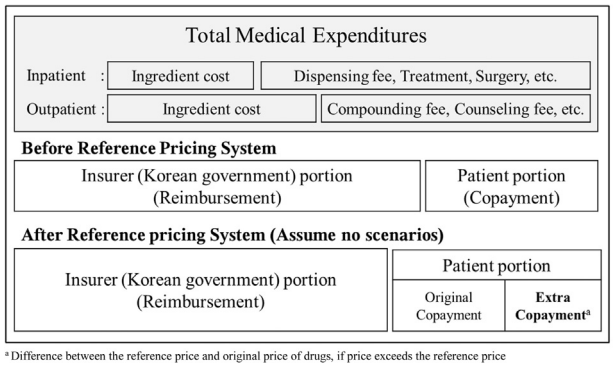


Fig. 1 – The diagram of Korea National Health Insurance before and after the reference pricing system.

pharmaceutical companies in tandem to reduce overall health expenditures [13].

A new type of policy, the reference pricing system (RPS), is being considered to encourage the use of low-cost drugs, promoting cost-consciousness among patients [14–16]. The RPS is a policy strategy that establishes a reimbursement level, or "reference price," within the same class of therapeutically interchangeable drugs, a "reference group" [15]. The third-party payer, in this case the NHI, reimburses only up to the established reference price for all products in a reference group, and patients are responsible for paying the difference between the reference price and the price of a more costly drug [14,15,17]. Various countries have accepted the RPS, using various groupings (such as chemical, therapeutic, or combined reference groups) and different levels of reimbursement (such as the lowest price, 30% less than the price of the original product, or the average price in a group) [18] (Appendix A). In 2002, the Korean government attempted to introduce a policy that would use the RPS, which would apply for only 11 therapeutic groups, but it was withdrawn because of health care providers, manufacturers, and patients' concern about the increased cost burden to patients and the small number of interchangeable generics [19,20]. The present Korean co-payment scheme sets a certain percentage of total medical expenditures that patients pay (Fig. 1) [4]. On the basis of the original proposal to institute the RPS in South Korea, if the drug price was higher than the reference value chosen, patients would have been required to pay the original co-payment rate plus the difference between the drug price and the reference price [21].

Reductions in pharmaceutical expenditures have been seen by other countries that have adopted the RPS [18] (Appendix B). The institution of the RPS was associated with a decrease in drug prices by 5% to 40%, subject to the reimbursement policy or pharmaceutical environment in various countries [15,16,22,23]. Prescription drug expenditures on specific classes decreased, and generic market shares increased across countries after introducing the RPS [16,24–26]. The RPS showed a switch to less expensive drugs, whereas studies based on a large number of patient-level observations showed no association between the introduction of the RPS and the health outcomes [16,27–29]. In 2012, the NHIC and the HIRA committees have reconsidered the RPS as a drug price reduction policy, noting that the RPS may cause patient behavior to change when they are responsible for a bigger share of the high-priced drugs, unlike previous drug price regulations [13]. In 2013, the HIRA report recommended that the RPS would encourage the use of low-priced drugs or generics, recommending that the policy should be considered as a long-term project after implementing a smaller pilot program for only one or two therapeutic groups [30]. The Korean NHIC also reported that the RPS would support the generic substitution in 2016 [31]. Nevertheless, because the potential effects of an RPS in Korea (for both the government and the patients) have not been estimated, the introduction of the RPS in Korea continues to be debated.

To our knowledge, no research has been conducted predicting the potential change in prescription drug expenditures under various scenarios after the introduction of an RPS in South Korea. Therefore, the purpose of this study was to predict the expected changes in prescription ingredient costs and co-payment rates after implementation of the RPS under various scenarios in South Korea.

Methods

Data Source

Data for this study were extracted from the Korean National Health Insurance Claims Database (KNHICD). These claims encompass medical utilization for about 97% of the South Korean population [32]. Korean health insurance includes payment for outpatient visits, inpatient visits, emergency care, and prescription drugs [4]. All drugs (except patented drugs [16], orphan drugs, and therapeutically noninterchangeable drugs), which were prescribed and dispensed in inpatient and outpatient settings for 4 months, for the months of January, April, July, and October in 2011 were included in this study. Prices of drugs, which were lowered after a new drug pricing regulation in 2012, were used to predict the effects of the RPS in the future.

Development of Models for the RPS in South Korea

To estimate the effect of possible RPS models, five features of a potential RPS policy were used when calculating the range of estimated costs: various levels of equivalence groupings, various methods of setting the reference price, inclusion of co-payment reduction programs, a reduction in prices by the manufacturers, and changes in prescribing patterns to less costly drugs.

First, in European countries, where implementation of the RPS is common, levels of equivalence (reference groups) are defined on the basis of the Anatomical Therapeutic Chemical (ATC) classification system [16,18]. The ATC codes are divided into different levels and grouped by their chemical, pharmacological, and therapeutic properties to function on the organ or system [33]. In this study, two categories of reference groups were used: 1) a chemical ingredient comparable group (chemical level), which used the same fifth level of ATC code (products with same active ingredient, e.g., amlodipine, felodipine, cimetidine, and ranitidine), dosage form, and dose (strength) and 2) a therapeutic and pharmacological comparable group (therapeutic level), which included the same fourth level of ATC code (chemically different but therapeutically and pharmacologically related products, e.g., selective calcium channel blockers and H2-receptor antagonists), dosage form, and dose (strength) [16] (Appendix C).

Second, the level of reimbursement (a reference price) was calculated using five methods:1) weighted average, the average for multiplications of drug price and quantity divided by quantity dispensed during study period; 2) mean, the arithmetic mean of all prices of drugs in a reference group; 3) mean without outliers, the arithmetic mean after removing prices higher than upper 10% and less than lower 10% for only reference groups including more than 10 drugs; 4) median, the median of all prices of drugs in a reference group; and 5) 33rd percentile, the price that is located at 33% from the minimum price within a reference group (note that the 33rd percentile is used for the German RPS). Many countries have accepted the lowest price as a reference price; this study, however, excluded the lowest price because it would be

improbable that Korea would choose this method on the basis of other pricing regulations in Korea.

Third, the Germany government gives a co-pay discount for patients who choose a product priced at least 30% lower than the reference price [13]. The Korean government may establish a co-pay reduction program for drugs priced lower than the reference price to encourage the use of generic drugs priced at the reference price or lower. In this study, it was assumed that this program would be applied for all drugs priced lower than the reference price, for drugs priced at least 10% lower than the reference price, or for drugs priced at least 20% lower than the reference price.

Fourth, there was a decline in prices for products that are included in the RPS in other countries [34]. Pharmaceutical companies may lower prices if their product is priced higher than the reference price to avoid loss of market share. For instance, in Germany, prices for antiulcerants decreased by 12.2% and prices of products were reduced by 11% in Sweden [16,35]. With reference to price reductions in other countries, this study assumed that pharmaceutical companies may lower their medications' price by 5%, 10%, or 15% to attract prescribers' or patients' demand so as not to lose market share.

Fifth, prescribers may change prescribing patterns to use lower priced drugs because patients may be sensitive to an additional co-payment [16]. In other countries, the RPS resulted in some switching from a more expensive drug to one with a price lower than the reference price. For instance, 9.3% of patients switched from high-priced cost-sharing calcium channel blockers to no-cost drugs after the RPS introduction in Canada [25]. In Germany, 48.7% of patients who were previously treated with atorvastatin with a price higher than the reference price switched to other statins included by the RPS [27]. The percentage of prescriptions switched to less expensive drugs by the prescriber was assumed to be 10%, 20%, or 30% in this study. Because of weak communication between physicians and patients, the percent change was not predicted to be more than 30%.

The three models (chemical-level model, therapeutic-level model, and hybrid groupings [the combination of chemical groups and therapeutic groups] model) for these analyses were developed using basic structures and scenarios. The chemical-level and therapeutic-level models covered all patients. The hybrid groupings model, however, was limited to outpatient prescription medication use because, according to the Korea Hospital Association, inpatients do not play a role in deciding what medications they receive while hospitalized compared with outpatients [36]. Similar to some European countries such as Germany and the Netherlands, a combination of possible changes for both chemical ingredient groups and therapeutic comparable groups was used [18]. The potential changes for therapeutic (ATC level 4) groups were applied for only the following groups: antihypertensives, cholesterol-lowering medications, peptic ulcer medications, and nonsteroidal anti-inflammatory drugs, which were the most frequently prescribed drug groups in 2011 [37]. All other potential changes were applied to chemical ingredient (ATC level 5) groups. In addition, the baseline co-payment rate was assumed to be discounted by 10% to lessen the impact of patients who would experience the RPS for the first time.

Calculation of Change in Prescription Drug Expenditures and Co-payment Rates

In the RPS, the third-party payer reimburses up to the reference price. The change in prescription ingredient costs was calculated by subtracting the reference price from the actual drug price, and then multiplying this difference by the quantity prescribed. In Equation 1, it was assumed that the quantity and pattern of medications prescribed would be the same before and after the RPS. For the therapeutic and pharmacological comparable group (ATC level 4), the daily cost (i.e., a reimbursement price × most frequent quantity per day) was used because dosing could differ between therapeutically similar medications.

$$C_1 = \sum (P_0 - P_1) Q_0. \quad (1)$$

$C_1$is the change in prescription ingredient costs; P_0 is the original price for all drugs; P_1 is the original price for all drugs if at reference price or lower, but same as reference price if higher than reference price; and Q_0 is the quantity prescribed during the study period. The prescription ingredient costs were defined as the total amount that pharmacies or hospitals pay for the drug products.

Patients may be required to pay the difference between the price of drug and the reference price if they want drugs that are priced higher than the reference price. Thus, the change in prescription ingredient costs would result in savings to the third-party payer (i.e., the government) but would increase the co-payment costs for patients. This would lead to a change in co-payment rates and reimbursement rates as calculated using the following equations:

$$CR(\%) = \left[\sum (C_0 + C_1) / \sum R\right] \times 100, \quad (2)$$

$$RR(\%) = 100 - CR(\%). \quad (3)$$

CR is co-payment rate, RR is reimbursement rate, R is total medical expenditures, C_0 is original co-payment, and C_1 is additional co-payment (change in ingredient costs). The total medical expenditures included ingredient costs, patient counseling fees, and compounding fees for outpatients, and dispensing fees, surgery or treatment fees, and clinical test costs for inpatients (Fig. 1). The total medical expenditures were used to calculate patients' overall co-payment rates.

If it is assumed that there will be no change in pricing and prescribing patterns, the total ingredient costs will not be different before and after the RPS. Nevertheless, on the basis of results from the RPS in European countries, it is expected that changes in pricing and prescribing will occur [16]. Equation 4 is proposed to identify how much savings in prescription ingredient costs might occur after the RPS:

$$\sum P_0 Q \sum P_0 Q_0 - \sum P_2 Q_1. \quad (4)$$

S is the savings in prescription ingredient costs under expected scenarios, P_2 is the decreased price by manufacturers if their original price is higher than the reference price, Q_1 is the change in quantity prescribed because of switching from high-cost drugs to reference-price drugs.

A co-pay reduction program would reduce patient co-payments only if they used drugs priced at the reference price or lower. The discounted co-payment was defined as the amount after the sum of quantity of drug multiplied by the difference between the reference price and the price of a drug is subtracted from the original co-payment, if a drug is priced lower than the reference price.

$$\sum (P_3 - P_4) Q_1 \sum (P_3 - P_4) Q_1), \text{ if drug price is lower than reference price.} \quad (5)$$

C_2 is the discounted co-payment under a co-pay reduction program, P_3 is the reference price, and P_4 is the price lower than the reference price.

The 2015 exchange rate (US $ 1 = 1027.75 Korean won) was applied. SAS 9.3 for Windows (SAS Institute, Inc., Cary, NC) and Microsoft Excel 2010 were used to estimate change in prescription drug expenditures because of the RPS.

Table 1 – Korea health insurance claim data.

	Total national health insurance claim data			Reference pricing system (level of equivalence)		
	Hospital or clinic	Community pharmacy	Total	Chemical level*	Therapeutic level*	Hybrid grouping model†
No. of active ingredients	1,903	1,544	2,097	1,034	887	819
No. of reference groups	NA	NA	NA	1,853	743	1,174
No. of products	12,457	10,406	13,323	8,109	7,578	6,094
Total ingredient cost ($)	1,334,993,979	2,619,775,237	3,954,769,216	2,487,561,372	2,292,403,211	1,789,292,568
Total medical expenditure‡ ($)	8,064,917,758	3,589,994,649	11,654,912,407	9,267,751,885	8,969,092,678	2,675,319,715
Co-pay rate (%)	18.4	25.4	20.8	20.4	20.4	25.4

NA, not applicable.
* These models included both inpatients and outpatients.
† This model included only outpatients of community pharmacies, and used combinations of chemical and therapeutic grouping.
‡ This includes ingredient cost, patient counseling fee, and compounding fee for outpatients, and dispensing fee, surgery or treatment fee, and clinical test cost for inpatients.

Results

We identified 13,323 individual drug products and 2,097 chemical ingredients in the KNHICD (Table 1). Total ingredient costs were $3,955 million and total medical expenditures were $11,655 million. Information from the national database showed that patients paid 20.8%, on average, for their health care services during 4 months in 2011. Among all prescribed drug products for both inpatients and outpatients, 8109 and 7578 products met our inclusion criteria for the analysis using the chemical grouping (ATC level 5) and the therapeutic grouping (ATC level 4), respectively. The KNHICD provided no actual ATC code, but an alternative code that corresponds with the ATC level 5. The alternative code was used for the chemical-level model. Nevertheless, missing observations were found when attempting to match drugs with the ATC level 4 code in the therapeutic-level model. The total ingredient costs were $2488 million and $2292 million for the chemical level and the therapeutic level, respectively. The hybrid grouping model that included only outpatient pharmacy claim data contained 6094 products, and the total ingredient cost for this model was $1789 million. The estimate rate of co-payment in the hybrid grouping model (25.4%) was higher than the co-payment rate in the chemical and therapeutic levels (20.4%).

The estimated changes in prescription ingredient costs are presented in Table 2. Change rates ranged from 1.4% to 7.5% according to the level of reimbursement (the reference price) at the chemical level. Change rates of the therapeutic-level groupings ranged from 10.3% to 22.8%, which were higher than those of the chemical-level groupings for all levels of reimbursement. The change rates of the hybrid grouping model fell between those of chemical-level and therapeutic-level groupings. The rates of the average of reference price to the highest price per reference group ranged from 36.7% to 53.9%. Although the analysis using the weighted average costs showed the lowest change rate, the analysis using the 33rd percentile showed the highest change rate for all cases because this scenario would result in a large difference between the price of drugs and the lower reference price.

Table 2 – Change in prescription ingredient costs by types of RPS.

Level of equivalence	Original total ingredient costs ($)	Level of reimbursement	Total ingredient costs under RPS ($)	Change* ($)	Change rate† (%)
Chemical level	2,487,561,372	Weighted average	2,452,142,006	35,419,366	1.4
	2,487,561,372	Mean	2,359,338,325	128,223,046	5.2
	2,487,561,372	Mean without outliers	2,377,759,283	109,802,089	4.4
	2,487,561,372	Median	2,390,953,565	96,607,807	3.9
	2,487,561,372	33rd percentile	2,300,233,495	187,327,877	7.5
Therapeutic level	2,292,403,211	Weighted average	2,056,802,344	235,600,866	10.3
	2,292,403,211	Mean	1,980,415,837	311,987,374	13.6
	2,292,403,211	Mean without outliers	1,971,534,981	320,868,230	14.0
	2,292,403,211	Median	2,006,339,135	286,064,075	12.5
	2,292,403,211	33rd percentile	1,769,925,743	522,477,468	22.8
Hybrid grouping model	1,789,292,568	Weighted average	1,714,142,280	75,150,288	4.2
	1,789,292,568	Mean	1,653,306,333	135,986,235	7.6
	1,789,292,568	Mean without outliers	1,658,674,211	130,618,357	7.3
	1,789,292,568	Median	1,674,777,844	114,514,724	6.4
	1,789,292,568	33rd percentile	1,601,416,849	187,875,720	10.5

RPS, reference pricing system.
* Change ($) = Original total ingredient costs − Total ingredient costs under RPS.
† Change rate(%) $= \frac{\text{Original total ingredient costs} - \text{Total ingredient costs under RPS}}{\text{Original total ingredient costs}}$.

Table 3 – Estimated additional co-payment and co-pay rate by types of RPS.

Original total medical expenditure ($)	Level of reimbursement (rate of average to highest price per group)	Insurer portion ($)	Patient portion ($)		Co-pay rate* (%)	Reimbursement rate† (%)
			Original co-payment	Additional co-payment		
		Chemical level‡				
9,267,751,885	Original price§	7,377,130,501	1,890,621,385	0	20.4	79.6
9,267,751,885	Weighted average (53.5%)	7,348,936,686	1,883,395,834	35,419,366	20.7	79.3
9,267,751,885	Mean (52.7%)	7,275,064,956	1,864,463,883	128,223,046	21.5	78.5
9,267,751,885	Mean without outliers (53.0%)	7,289,728,038	1,868,221,758	109,802,089	21.3	78.7
9,267,751,885	Median (53.8%)	7,300,230,686	1,870,913,392	96,607,807	21.2	78.8
9,267,751,885	33rd percentile (50.8%)	7,228,017,510	1,852,406,498	187,327,877	22.0	78.0
		Therapeutic level‡				
8,969,092,678	Original price	7,139,397,772	1,829,694,906	0	20.4	79.6
8,969,092,678	Weighted average (44.7%)	6,951,859,482	1,781,632,330	235,600,866	22.5	77.5
8,969,092,678	Mean (46.5%)	6,891,055,822	1,766,049,482	311,987,374	23.2	76.8
8,969,092,678	Mean without outliers (46.2%)	6,883,986,661	1,764,237,787	320,868,230	23.2	76.8
8,969,092,678	Median (42.4%)	6,911,690,768	1,771,337,835	286,064,075	22.9	77.1
8,969,092,678	33rd percentile (36.7%)	6,723,505,708	1,723,109,503	522,477,468	25.0	75.0
		Hybrid grouping model‖				
2,675,319,715	Original price	2,063,741,628	611,578,087	0	22.9	77.1
2,675,319,715	Weighted average (53.1%)	2,005,770,696	594,398,731	75,150,288	25.0	75.0
2,675,319,715	Mean (51.7%)	1,958,841,846	580,491,633	135,986,235	26.8	73.2
2,675,319,715	Mean without outliers (52.3%)	1,962,982,627	581,718,730	130,618,357	26.6	73.4
2,675,319,715	Median (53.9%)	1,975,404,970	585,400,021	114,514,724	26.2	73.8
2,675,319,715	33rd percentile (48.4%)	1,918,814,298	568,629,697	187,875,720	28.3	71.7

RPS, reference pricing system.

* Co-pay rate(%) $= \frac{\text{Original co-payment} + \text{Additional co-payment}}{\text{Total medical expenditures}}$.

† Reimbursement rate (%) = 100 (%) – Co-pay rate (%).

‡ 20.4% is a baseline co-pay rate of chemical and therapeutic levels.

§ The price when there is no impact of RPS.

‖ 22.9% is a baseline co-pay rate of the hybrid grouping model (combination of chemical and therapeutic groupings).

Overall reimbursement rates for the government were decreased and co-payment rates for patients were increased regardless of the type of RPS because of the extra co-payment of high-cost drugs to patients (Table 3). At the chemical level, all co-payment rates were higher (20.7–22.0%) than the baseline co-payment rate (20.4%). Co-payment rates for therapeutic levels were increased up to 25.0% when the 33rd percentile was used as a reference price. The hybrid grouping model had co-payment rates ranging from 25.0% to 28.3% depending on various reference prices (baseline was 22.9%).

Assuming these different scenarios, such as changes in pricing and prescribing, were plausible after introducing the RPS in South Korea, savings rates of prescription ingredient costs from the social perspective were estimated to range from 1.6% to 13.7% (Fig. 2). Using the 33rd percentile as the level of reimbursement showed the highest savings rates for both the therapeutic-level and the hybrid grouping model.

Instead of only estimating changes in percentages of co-payments (i.e., co-payment rates), the authors also assessed changes in absolute co-payment—in dollars. Co-payment dollars were less than the original co-pay amount depending on the types of co-payment reduction program instituted (Fig. 3). In the hybrid grouping model, all scenarios that included a co-pay reduction program showed a smaller co-payment than baseline ($612 million). Co-payments for chemical level or the hybrid grouping model were estimated to be lower than the original co-payment without a co-payment reduction program, assuming a decline in prices by 15% and a switch of 30% of the prescriptions to drugs priced lower than the reference price. The co-pay reduction program could help decrease co-payment rates lower than the baseline (Appendices D and E).

Discussion

This study assessed the effects of the RPS that may occur after the introduction of the policy in South Korea. Our literature review has indicated that savings rates for drug expenditures were 2.1% to 18%, although each study analyzed different classes of drugs in different reimbursement systems (Appendix B). This is consistent with our findings that the establishment of an RPS policy in South Korea may reduce prescription ingredient costs by 1.6% to 13.7%, assuming similar shifts that have been reported in other countries. Regarding patient costs, this study found that a co-pay reduction program and reductions in "co-pay rate designated by law" could be used to lessen patients' financial burden. The results provided that the price reduction, switching to less costly drugs, and discount program may deter cost-shifting to patients.

The reference group is usually defined by an active ingredient substance class (ATC level 5), a therapeutic class (ATC level 4), or a combination of these methods [18]. Estimated savings in ingredient costs were different depending on the criteria used to cluster these medications. In European countries, the therapeutic level generally showed greater magnitude in price reduction than the chemical level [38,39]. We also found that the therapeutic group had a larger savings rate than the chemical group for all scenarios. When a difference between the price of

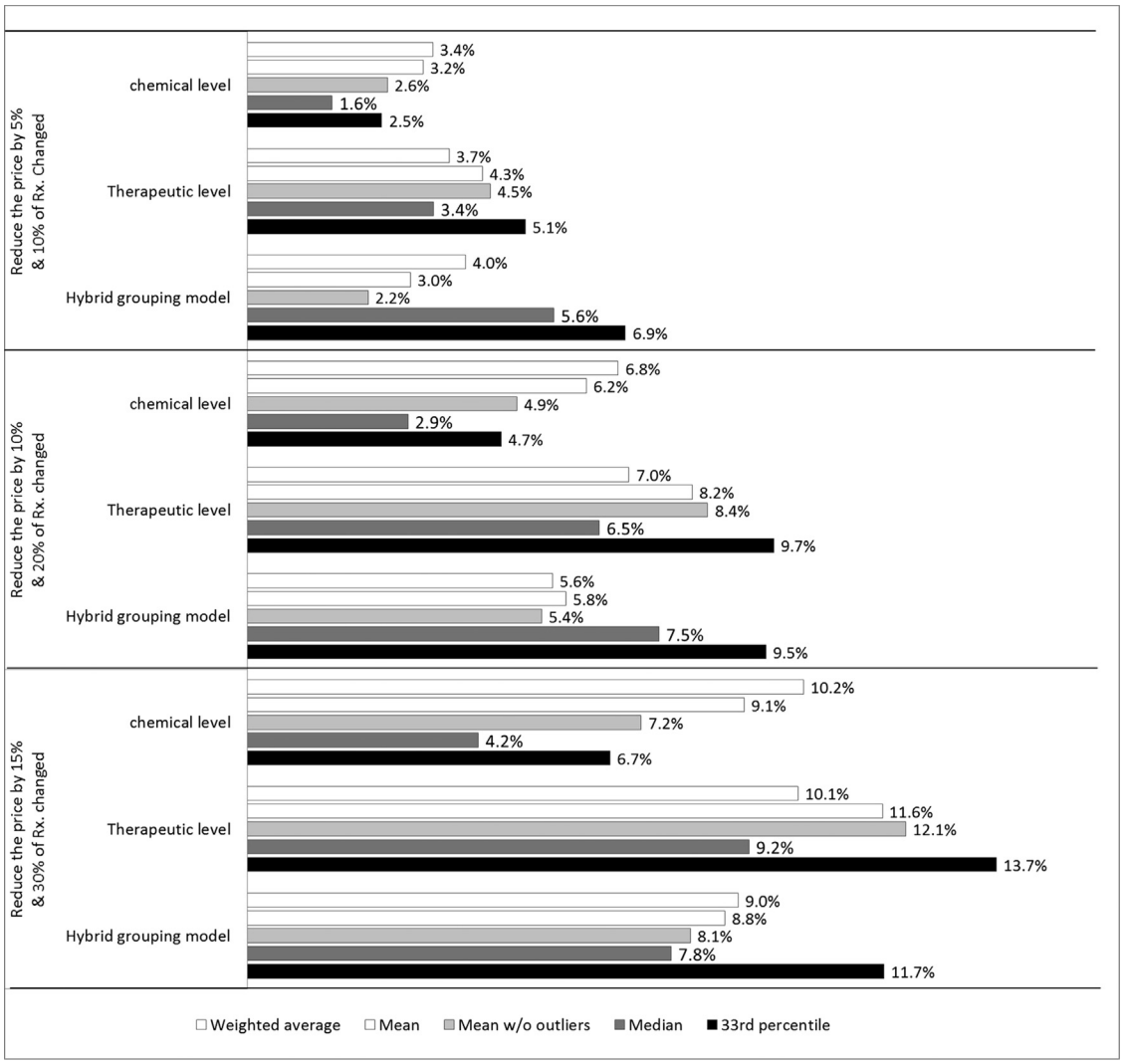
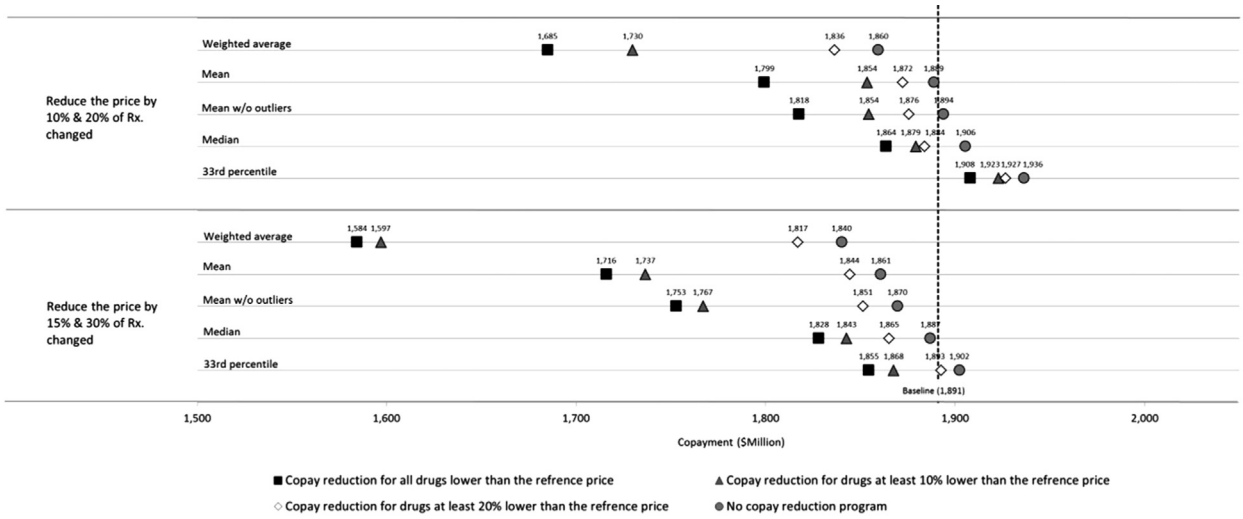


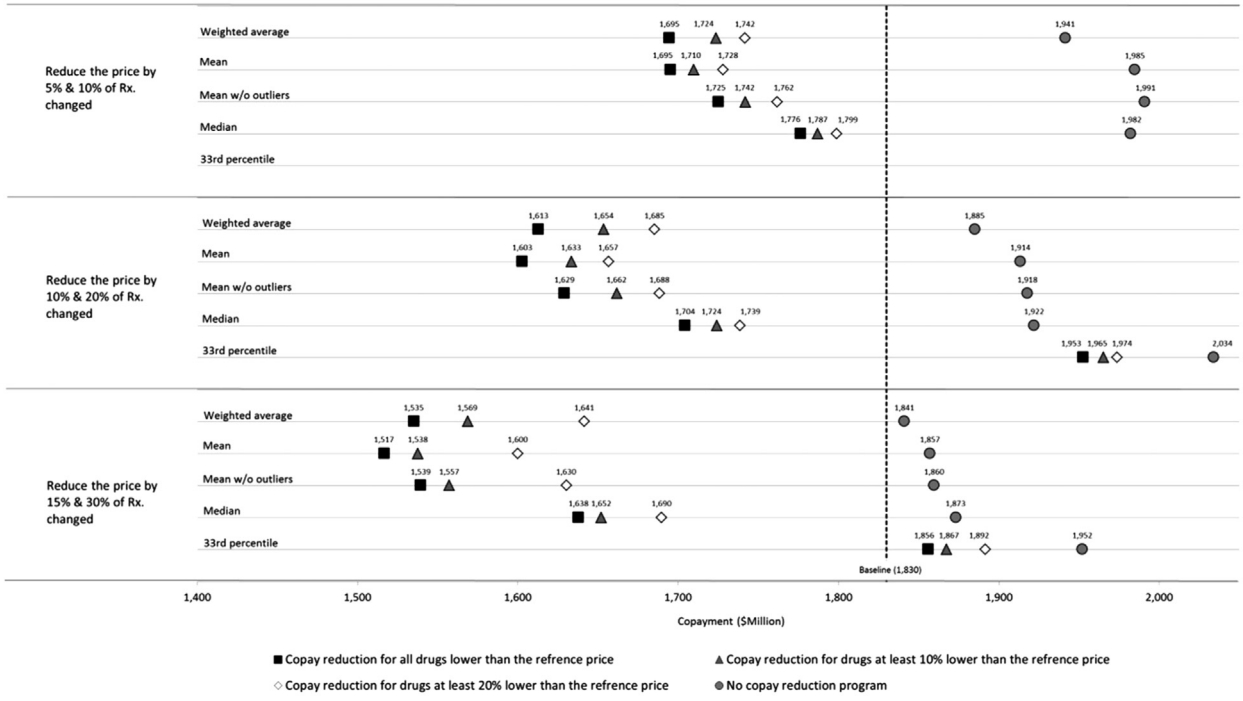
Fig. 2 – Savings rate on prescription ingredient costs for chemical-level model, therapeutic- level model, and hybrid grouping model under scenarios.
Note. **Savings rate**$(\%) = \frac{\text{Original prescription ingredient costs (\$)} - \text{Prescription ingredient costs under expected scenarios (\$)}}{\text{Original prescription ingredient costs (\$)}}$.

the most expensive drug and the least expensive drug is large, potential savings are greater [16].The therapeutic group generally has a larger variance in price because of having a greater number of interchangeable drugs than the chemical group. In addition, savings at the chemical level would not be significant in Korea because the government has already seen a reduction in the prices of listed drugs on the basis of the rule that medications with the same ingredients are required to be priced the same [1]. Our results showed that applying changes only at the therapeutic level would lead to significant savings for the third-party payer (i.e., the government), but it would result in an increase in co-payment for patients. There have been debates about whether all drugs in therapeutic groupings are, in fact, interchangeable. Changes in savings and co-payments in the hybrid grouping model were estimated to fall between those in the chemical level and the therapeutic level. Germany and Hungry introduced only chemical groupings in the beginning, and scaled up to add classes with therapeutic comparability in their RPS [34]. Korea may also move progressively to therapeutic groupings for specific classes after applying chemical groupings in the beginning.

Most European countries define the reference price around or lower than the average price or at the lowest price in the reference group [40]. A lower reference price usually results in higher savings for the government; the mechanism to set the reference price, however, should be chosen carefully because it may lead to patient financial burden when patients do not have enough information about medications or the patients' choices are limited. In this study, the 33rd percentile resulted in the highest co-payment rate (up to 28.3%) for patients. Several European countries experienced that the RPS may generate savings only at its introduction point, and may be limited to the "one-off" impact of the introduction because the policy may discourage price competition in the long-term [21,34]. Generic manufacturers did not show a voluntary price reduction if a drug had a price lower than the reference price even when there were other lower priced drugs in the same reference group [22,41]. If the manufacturers have prices higher than the reference price, they set a

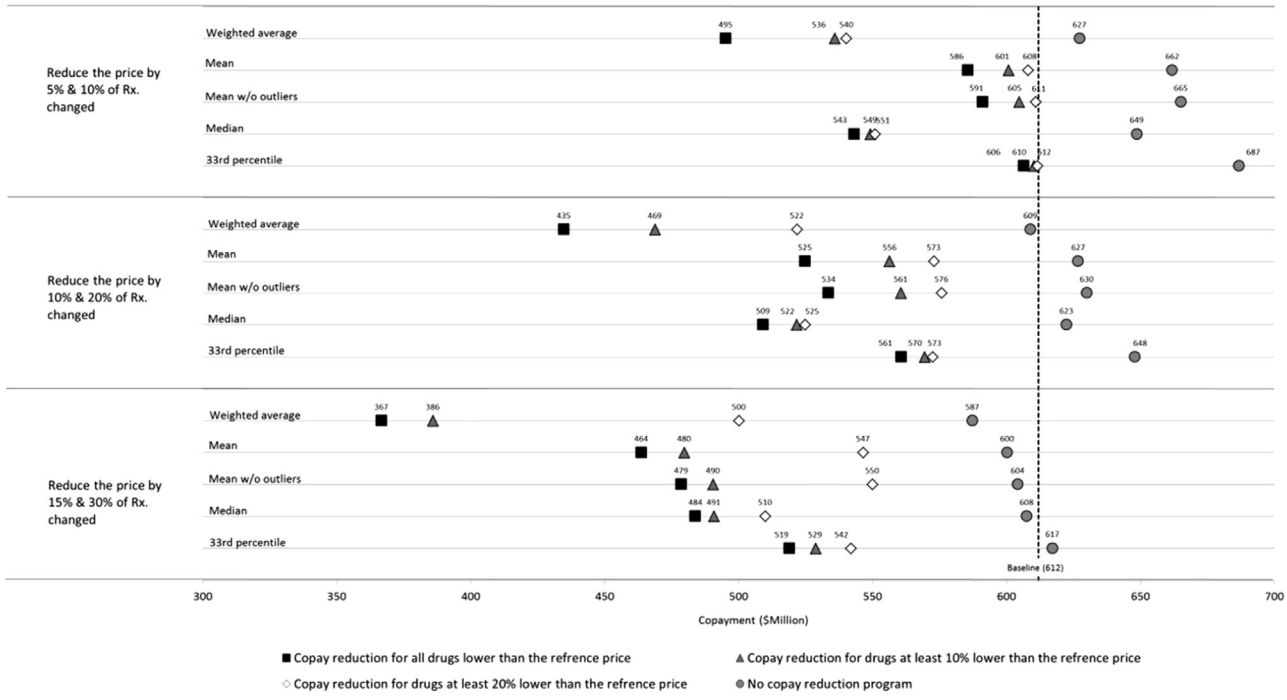


(A) Chemical level



(B) Therapeutic level

Fig. 3 – Patient co-payments for chemical-level, therapeutic-level, and hybrid grouping models under scenarios.
Note. **Baseline represents original co-payments for patients before the reference pricing system. Baseline co-pay rate: chemical level, 20.4%; therapeutic level, 20.4%; hybrid grouping model, 22.9%.**



(C) The Hybrid Grouping Model

Fig. 3 – Continued.

drug price close to the level of the reference price rather than reduce prices to be lower than the reference price [22]. In Korea, the government has already introduced other drug pricing regulations, which may cause manufacturers to oppose further reductions sought by the introduction of RPS. Thus, the reference price may need to be revisited and adjusted over time on the basis of market changes to continue to show savings. For example, German policymakers have reduced the reference prices 5 times between 1995 and 2005 [42]. In Belgium, the government has progressively reduced the reference prices between 2001 and 2003 [43].

Policymakers should encourage generic substitution to achieve the aim of RPS, which is to not only save on drug expenditures but also help patients to continue to benefit from the drugs. Generic substitution is used to allow health care providers to substitute a generic product for a brand name product within the interchangeable group [44]. It provides companies with incentives to reduce prices to have their products dispensed because it enhances price competition when more expensive drugs are substituted with cheaper alternatives [21]. It is necessary to provide regulations, and also to have educational campaigns about this new policy to promote the use of low-cost drugs. In Italy, if a product is priced higher than the reference level, pharmacists must inform patients that cheaper substitutes are available, unless the prescriber notes "not-substitutable" on the prescription [17].In Korea, physicians prefer to prescribe expensive generic drugs [12,45]. The patient's role in the pharmaceutical market is usually limited because physicians can choose a prescription drug on behalf of patients who have limited professional medical information [21]. The physician-patient communication is more limited in Korea because the relationship between a physician and a patient is practically vertical in the Korean society [46]. We recommend the implementation of a hybrid grouping model for outpatient medications—rather than for inpatient medications—because patients do not have much say in choosing inpatient medications.

All products in the same reference group must have bioequivalence to promote a substitution. If drugs are not interchangeable in benefit and risk, substitution may result in negative impacts on health outcomes and increase the use of other health care services [47]. In many countries with RPS, the policy leads to a change in prescribing patterns, and achieved cost savings without any measurable negative effect on patient health outcomes and utilization [15,18].

The effect of the RPS on research and development is still controversial. Some argue that the RPS may limit the incentives for manufacturers to invest in the research and development of new products. Nevertheless, the RPS might lead manufacturers to look for innovative investments to increase expected profit rather than "me-too" drug [16,48].

Study Limitations

Our study had a few limitations. The first limitation is that our study was constrained by the short time frame. The change in prescription drug expenditures could not be estimated in the longitudinal analysis. If the government changes the reference prices over time, or there is a change in morbidity of patients, the prediction of the effects of the RPS would need adjustment. Because this study assumed that total demand was equal before and after the RPS, other potential influences, such as the change in co-payment rates, were not considered.

Second, assumed scenarios could be modified to be more suitable for the pharmaceutical environment in South Korea, because they are based on experiences of other countries with the RPS. Although the parameters used in the scenarios were determined on the basis of the effect of the RPS in other countries, they may not represent the situation accurately in

Korea after the RPS. The percentage of prescriptions switched to less costly drugs may be lower in South Korea because of long-term beliefs and established patterns. A survey of physicians, pharmacists, and patients, which would assess their perception of generic substitution, may be of benefit.

Third, specific therapeutic classes may show different changes. Previous studies that reported the effect of RPS analyzed specific classes such as proton pump inhibitors, or statins [27,49]. Because this study was designed to analyze nationwide drug expenditures, we could not compare the results of the same therapeutic classes with other studies.

Conclusions

This study predicted potential changes in prescription ingredient costs and co-payment rates, applying scenarios that included various levels of equivalence groupings, reference pricing techniques, a co-pay reduction program, a reduction in manufacturer prices, and prescription switches to less costly drugs, after the introduction of the RPS in South Korea. Our predictions indicated that there would be savings in prescription drug expenditures for the third-party payer (government) but an RPS policy may result in an additional financial burden for patients. In some scenarios, however, patients would also save money because of reduced manufacturer pricing, switching to lower priced medications, or a government-supported co-pay reduction program. In the hybrid grouping model, cost-shifting to patients was limited and both the patient and the government could save on drug expenditures even without a co-pay discount. Cooperation between the government, manufacturers, health care providers, and patients is essential to achieve positive effects of the RPS.

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Appendix A – Application of RPS in various countries.

Country	Year started*	Reference group (level of equivalence)	Reference price (level of reimbursement)
Australia [16]	1990 (level 1) 1998 (level 2)	Chemical, pharmacological, and therapeutic	Lowest price in group
Belgium [16,22,43]	2001	Chemical	30% less than the price of the original product
Canada [15,16]	1994 (level 1) 1995 (level 2)	Chemical, pharmacological, and therapeutic	Lowest price in group
Czech Republic [22]	1995	Chemical, pharmacological, and therapeutic	Lowest price in group
Denmark [22]	1993	Chemical	Lowest price in reimbursement or substitution group
Finland [22]	2009	Chemical	Lowest price plus €1.5
France [22]	2003	Chemical	Average of generics with one active ingredient
Germany [15,16,50]	1989 (level 1) 1991 (level 2) 1992 (level 3)	Chemical, pharmacological, and therapeutic	Price cap of 33rd percentile price-in-price range of group with chemical equivalence
Greece [22]	2006	Pharmacological	Lowest price in group
Hungary [16,34]	1997 (level 1) 2003 (level 2)	Chemical, pharmacological, and therapeutic	Lowest price in group
Italy [16]	2001	Chemical	Lowest price in group
Netherlands [22,23]	1991	Chemical, pharmacological, and therapeutic	Lowest price in group
New Zealand [16]	1993	Therapeutic	Lowest price in group
Poland [22]	1998	Chemical, pharmacological	Lowest price in group
Portugal [22]	2003	Chemical	Price of most expensive generic
Spain [15,16]	2000	Chemical	Average of the prices of three cheapest products

RPS, reference pricing system.
* Level 1: chemical; level 2: pharmacological or therapeutic; level 3: therapeutic combinations grouping.

Appendix B – Effect of RPS in various countries.

Country	Price	Quantity or expenditures	Utilizations and others
Australia [16]	–	–	Usage rate of generic drugs increased 4.5– 11.0%
Belgium [16,43]	Not significant	Expenditures: decreased by 2.1%	Switch to less costly drugs Market share of generics increased
Canada [15,16,25,28]	Not significant (calcium channel blocker not changed)	Significant saving (ACE inhibiters decreased by 6%;calcium channel blocker and proton pump inhibitors decreased by 12%)	Switch to less costly drugs Use of medical services increased Prescription duration increased No effect on health
Denmark [22]	Not significant	Expenditures: decreased by 1.5%	–
France [22]	Decreased	–	–
Germany [15,16,26,27]	Decreased by about 20% (antidiabetics decreased by 18.70%; anti-ulcerants decreased by 12.20%; brand name drugs decreased by 27%)	Quantity: decreased by 4.1% Expenditures: statins decreased by 18%	Switch to less costly drugs Use of medical services was ambiguous Effect on health (mortality and hospitalization rates) was not significant
Hungary [16]	Not significant	Significant saving	Switch to less costly drugs Market share of generics increased
Italy [16,29]	Decreased by 40% compared with average in the EU	Expenditures: decreased by 5%	Switch to less costly drugs Market share of generics increased
Netherlands [22,23]	Decreased by 5%(1991–1993)	–	–
New Zealand [22]	Not significant	Not significant	Effect on health was negative
Spain [15,16]	Decreased/not significant(ranitidine decreased by 19.2%; omeprazole not changed; fluoxetine decreased by 10%)	Expenditures: decreased by 4%	Switch to less costly drugs Market share of generics increased

ACE, angiotensin-converting enzyme; RPS, reference pricing system.

Appendix C – Examples for the fourth and fifth levels of the ATC code.

ATC code (fourth level)	ATC code (fifth level)	Active ingredient
C08CA	C08CA01	Amlodipine
Selective calcium channel blockers	C08CA02	Felodipine
	C08CA03	Isradipine
	C08CA04	Nicardipine
	C08CA05	Nifedipine
	C08CA06	Nimodipine
	C08CA07	Nisoldipine
	C08CA08	Nitrendipine
	C08CA09	Lacidipine
	C08CA10	Nilvadipine
	C08CA11	Manidipine
	C08CA12	Barnidipine
	C08CA13	Lercanidipine
	C08CA14	Cilnidipine
	C08CA15	Benidipine
	C08CA16	Clevidipine
	C08CA55	Nifedipine, combinations
A02BA	A02BA01	Cimetidine
H2-receptor antagonists	A02BA02	Ranitidine
	A02BA03	Famotidine
	A02BA04	Nizatidine
	A02BA05	Niperotidine
	A02BA06	Roxatidine
	A02BA07	Ranitidine bismuth citrate
	A02BA08	Lafutidine
	A02BA51	Cimetidine, combinations
	A02BA53	Famotidine, combinations

ATC, Anatomical Therapeutic Chemical.

Appendix D – Estimated additional co-payment and co-payment rate by scenarios.

Co-pay reduction program				No co-pay reduction program		For drugs at least 20% lower than the reference price		For drugs at least 10% lower than the reference price		For all drugs lower than the reference price	
Change in price and Rx	Level of reimbursement	Total medical expenditures ($)	Original co-payment* ($)	Additional co-payment ($)	Co-pay rate† (%)	Additional co-payment ($)	Co-pay rate† (%)	Additional co-payment ($)	Co-pay rate† (%)	Additional co-payment ($)	Co-pay rate† (%)
				Chemical level							
Reduce the price by 5% and 10% of Rx changed	Weighted average	9,182,079,299	1,870,834,923	11,319,874	20.5	−11,867,672	20.2	−18,305,035	20.2	−85,672,586	19.4
	Mean	9,187,566,042	1,860,395,641	67,979,567	21.0	51,588,421	20.8	47,052,299	20.8	22,379,956	20.5
	Mean without outliers	9,203,887,132	1,865,085,408	61,311,603	20.9	42,983,216	20.7	38,708,830	20.7	18,633,909	20.5
	Median	9,229,007,054	1,870,204,116	61,339,820	20.9	39,647,774	20.7	36,773,534	20.7	30,179,518	20.6
	33rd percentile	9,206,408,173	1,851,762,238	129,142,301	21.5	119,412,308	21.4	117,733,885	21.4	113,443,931	21.3
Reduce the price by 10% and 20% of Rx changed	Weighted average	9,097,795,184	1,855,030,406	4,508,879	20.4	−18,678,667	20.2	−125,115,057	19.0	−169,955,729	18.5
	Mean	9,113,147,166	1,851,460,530	37,360,253	20.7	20,969,107	20.5	2,180,491	20.3	−52,039,893	19.7
	Mean without outliers	9,144,702,505	1,858,220,766	35,777,183	20.7	17,448,796	20.5	−3,753,831	20.3	−40,549,745	19.9
	Median	9,194,499,635	1,868,012,766	37,574,313	20.7	15,883,240	20.5	11,223,547	20.4	−4,327,901	20.3
	33rd percentile	9,151,945,512	1,849,194,547	87,266,359	21.2	77,537,339	21.1	73,711,506	21.0	58,982,243	20.8
Reduce the price by 15% and 30% of Rx changed	Weighted average	9,013,727,074	1,838,428,548	1,822,428	20.4	−21,365,118	20.2	−241,439,066	17.7	−254,024,811	17.6
	Mean	9,041,036,244	1,840,173,688	20,576,989	20.6	4,185,843	20.4	−103,500,851	19.2	−124,150,815	19.0
	Mean without outliers	9,088,149,842	1,849,963,108	19,703,235	20.6	1,374,848	20.4	−82,935,539	19.4	−97,102,408	19.3
	Median	9,162,392,605	1,864,571,910	22,334,225	20.6	642,180	20.4	−21,765,994	20.1	−36,435,904	20.0
	33rd percentile	9,102,270,980	1,845,202,876	57,158,842	20.9	47,429,822	20.8	22,372,172	20.5	9,307,711	20.4
				Therapeutic level							
Reduce the price by 5% and 10% of Rx changed	Weighted average	8,884,288,008	1,779,319,461	162,133,787	21.9	−37,571,394	19.6	−55,803,454	19.4	−84,803,697	19.1
	Mean	8,870,290,440	1,764,592,358	220,327,901	22.4	−36,658,721	19.5	−54,930,674	19.3	−69,289,224	19.1
	Mean without outliers	8,866,931,647	1,762,149,519	228,943,809	22.5	−494,284	19.9	−20,171,248	19.6	−37,041,109	19.5
	Median	8,890,792,508	1,770,504,239	211,850,158	22.3	28,414,498	20.2	16,434,931	20.1	5,941,134	20.0
	33rd percentile	8,852,205,303	1,722,469,608	408,726,830	24.1	348,327,901	23.4	342,243,736	23.3	336,468,013	23.3
Reduce the price by 10% and 20% of Rx changed	Weighted average	8,807,801,508	1,774,177,927	110,850,888	21.4	−88,854,293	19.1	−120,590,611	18.8	−161,291,170	18.3
	Mean	8,782,144,490	1,760,300,567	153,220,141	21.8	−103,767,453	18.9	−126,891,754	18.6	−157,435,174	18.3
	Mean without outliers	8,775,576,745	1,757,519,895	160,283,143	21.9	−69,154,950	19.2	−95,816,103	18.9	−128,396,011	18.6
	Median	8,821,084,894	1,768,096,335	153,945,999	21.8	−29,490,635	19.7	−43,966,918	19.5	−63,766,480	19.3
	33rd percentile	8,747,772,318	1,720,593,066	313,492,581	23.3	253,092,678	22.6	244,586,719	22.5	232,036,001	22.3
Reduce the price by 15% and 30% of Rx changed	Weighted average	8,737,042,082	1,767,275,372	73,927,512	21.1	−125,778,643	18.8	−198,551,204	18.0	−232,050,596	17.6
	Mean	8,702,040,379	1,754,230,488	102,871,321	21.3	−154,115,300	18.4	−216,599,368	17.7	−237,539,285	17.4
	Mean without outliers	8,692,378,497	1,751,088,759	108,610,071	21.4	−120,828,022	18.8	−193,791,292	17.9	−211,594,259	17.7
	Median	8,758,230,114	1,764,506,411	108,688,883	21.4	−74,747,750	19.3	−112,374,605	18.9	−126,622,233	18.7
	33rd percentile	8,654,208,708	1,717,637,920	234,414,984	22.6	174,016,054	21.9	149,659,937	21.6	138,471,418	21.4

* Baseline co-pay rate = 20.4%.

† Co-pay rate(%) = $\frac{\text{Original co-payment (\$)} + \text{Additional co-payment (\$)}}{\text{Total medical expenditures (\$)}}$.

Appendix E – Estimated Additional Copayment and Copayment Rate by Scenarios under the Hybrid Grouping Model.

Co-pay reduction program				No co-pay reduction program		For drugs at least 20% lower than the reference price		For drugs at least 10% lower than the reference price		For all drugs lower than the reference price	
Change in price and Rx	Level of Reimbursement	Total medical expenditures ($)	Original Co-payment* ($)	Additional Co-payment ($)	Co-pay rate† (%)	Additional co-payment ($)	Co-pay rate† (%)	Additional co-payment ($)	Co-pay rate† (%)	Additional co-payment ($)	Co-pay rate† (%)
Reduce the price by 5% and 10% of Rx Changed	Weighted average	2,602,859,645	585,411,514	42,004,378	24.1%	-45,105,327	20.8%	-49,464,364	20.6%	-90,148,382	19.0%
	Mean	2,621,735,831	580,767,002	81,197,762	25.2%	27,361,712	23.2%	20,085,624	22.9%	4,910,727	22.3%
	Mean w/o outliers	2,635,608,854	583,937,486	81,201,654	25.2%	26,938,458	23.2%	20,790,075	22.9%	7,276,089	22.4%
	Median	2,574,735,101	570,769,548	77,930,431	25.2%	-19,752,858	21.4%	-21,570,421	21.3%	-27,583,556	21.1%
	33rd percentile	2,551,238,142	552,467,090	134,496,716	26.9%	59,129,166	24.0%	57,921,674	23.9%	53,984,919	23.8%
Reduce the price by 10% and 20% of Rx Changed	Weighted average	2,575,318,901	582,713,467	26,266,115	23.6%	-60,843,590	20.3%	-113,876,916	18.2%	-147,847,239	16.9%
	Mean	2,570,863,537	576,105,809	50,715,641	24.4%	-3,120,409	22.3%	-19,676,964	21.6%	-51,257,602	20.4%
	Mean w/o outliers	2,578,733,155	577,457,724	52,671,369	24.4%	-1,590,854	22.3%	-16,792,994	21.7%	-43,819,022	20.7%
	Median	2,540,256,872	568,302,825	54,242,763	24.5%	-43,440,525	20.7%	-46,654,342	20.5%	-59,083,435	20.0%
	33rd percentile	2,505,157,869	550,376,493	97,561,664	25.9%	22,195,086	22.9%	19,165,167	22.7%	10,467,526	22.4%
Reduce the price by 15% and 30% of Rx changed	Weighted average	2,513,742,642	570,890,771	16,407,687	23.4%	-70,702,019	19.9%	-184,904,889	15.4%	-204,112,868	14.6%
	Mean	2,518,701,046	568,488,552	31,874,483	23.8%	-21,961,567	21.7%	-88,659,694	19.1%	-104,751,155	18.4%
	Mean w/o outliers	2,529,983,946	570,679,242	33,574,313	23.9%	-20,687,910	21.7%	-80,202,384	19.4%	-91,989,297	18.9%
	Median	2,536,298,711	571,548,712	36,085,624	24.0%	-61,597,665	20.1%	-80,710,289	19.4%	-87,585,502	19.1%
	33rd percentile	2,466,365,361	547,952,476	69,372,902	25.0%	-5,993,676	22.0%	-19,075,651	21.4%	-28,943,809	21.0%

* Baseline co-pay rate = 22.9%.

† Co-pay rate(%) $= \frac{\text{Original co-payment (\$)} + \text{Additional co-payment (\$)}}{\text{Total medical expenditures (\$)}}$.

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