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[Title Page]

A single pill combination of antihypertensives does improve adherence: A Korean nationwide study

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Abstract

Objectives: We tried to clarify whether single pill combination (SPC) of antihypertensives actually improves adherence using a representative national data in a real-world setting.

Design: A nationwide population-based study

Setting: We used a 2.2% cohort (N=1,048,061) of total population (N=46,605,433) that was randomly extracted by National Health Insurance of Korea from 2008 to 2013.

Participants: We included patients (N=116,677) who were prescribed with same antihypertensive drugs for at least one year and divided them into groups of ARB (Angiotensin-II-receptor-blocker) alone, CCB (Calcium-channel-blocker) alone, multiple pill combination (MPC) and SPC of ARB/CCB.

Primary outcome measures: Medication possession ratio (MPR), a frequently used indirect measurement method of medication adherence.

Results: Adjusted MPR was higher in combination therapy (89.7% in SPC, 87.2% in MPC) than monotherapy (81.6% in ARB, 79.7% in CCB), and MPR of SPC (89.7%, confidence interval, [CI] 89.3-90.0) was higher than MPR of MPC (87.2%, CI 86.7-87.7) ($p<0.05$). In subgroup analysis, adherences of SPC and MPC were 92.3% (CI 91.5-93.0) versus 88.1% (CI 87.1-89.0) in aged 65-74 years and 89.3% (CI 88.0-90.7) versus 84.8% (CI 83.3-92.0) in 75 years or older($p<0.05$). According to total pill numbers, adherences of SPC and MPC were 90.9% (CI 89.8-92.0) versus 85.3% (CI 84.1-86.5) in 7-8 pills and 91.2% (CI 89.3-93.1) versus 82.5% (CI 80.6-84.4) in 9 or more ($p<0.05$). The adherence difference between SPC and MPC started to increase

at 5-6 pills and at 50-64 years ($p<0.05$). When analyzed according to elderly status, the adherence difference started to increase at 3-4 pills in the elderly (65 years and older) and at 5–6 in the non-elderly group (20-64 years) ($p<0.05$). These difference all widened further with increasing age and the total medications.

Conclusion: SPC regimen demonstrated higher adherence than MPC and this tendency is more pronounced with increasing age and total medications.

Keywords hypertension, medication adherence, angiotensin II receptor blocker, calcium channel blocker, single pill combination

Strengths and limitations of this study

- Strength of this study is that we not only compared the adherence between combination and monotherapy of antihypertensive medications but also the adherence of single pill combination (SPC) and multiple pill combination (MPC) regimen in a real world by using National Health Insurance Service National Sample Cohort (NHIS-NSC), a representative large scale health insurance claim data of Korea accounting for 2.2% of total population.
- Another strength of this study is that we analyzed the differences in medication adherence of subjects who continued to take antihypertensive drugs for at least one year for the maximum of six observed years.
- NHIS-NSC could not provide detailed information regarding some specific factors that could affect the medication adherence such as education level, occupation, caregiver status, the family environment, and healthcare provider factors.
- We did not specify comorbidities according to severity, and only adjusted with the average number of diagnoses of the subject during the observation period.

Introduction

Adherence to medication is an explanation of drug taking behavior, and refers to taking the drug over the time, dose, and frequency prescribed by the healthcare provider (1). The World Health Organization (WHO) defines medication non-adherence as a medically ill state, because when medication adherence is low, the illness progresses and health outcome is low (1). Non-adherence may lead to various clinical risks. In many studies, low adherence is associated with higher mortality and hospitalization rates than higher adherence (2-4). Also in terms of health economics, non-adherent patients use healthcare resources more than do adherent patients, and consequently, the burden of social illness increases because of the increase in additional medical expenses (5-7). Non-adherence is observed more frequently for chronic than acute diseases, especially for hypertension, for which non-adherence is reported in 50–70% of cases (1, 7-9).

Adherence to medication is determined by the complexity of various aspects such as factors associated with the patient, condition, therapy, the healthcare system, and the social/economic status etc. (1, 5, 7, 10); thus, a strategic approach to the specific cause is needed to improve adherence. Among these many factors, there were some previous studies relating a lower number of medications taken by a patient with higher adherence in chronic diseases such as hypertension (11-15). This implies that selecting a single pill combination (SPC) prescription could increase adherence compared to a multiple pill combination (MPC) prescription (11-15). However, most previous research reported results obtained under certain center

conditions or were short-term studies of small samples, and systematic field surveys using real-world representative data were not common. Therefore, the aim of this study was to investigate the effect of SPC on the adherence to antihypertensive medication in a real-world setting. In order to do this, we first checked the overall medication prescription status of hypertensive patients and investigated the relation between multiple medication prescriptions, age, and medication adherence to antihypertensive agents.

Methods

Data source

The data used in this study were obtained from a sample of the Korean National Health Insurance Service National Sample Cohort (NHIS-NSC). This data is a sample of 1,048,061 individuals, around 2.2% of the total population (N=46,605,433), and provides national health information according to sex, age, and income. In addition, this cohort data is obtained through continuous observation every year, and include qualification data (birth, death, sex, family relationship, address, property, income, insurance type), medical service use data (billing statement, medical record, diagnosis record, prescription record, etc.), and health examination data (Supplementary Figure 1) (16).

Study population

In total, 206,739 hypertension patients taking antihypertensive medications were selected from the 2008 to 2013 NHIS-NSC (N=1,048,061, total outpatient prescriptions: 221,750,977 cases). Hypertension diagnosis was defined as all patients with the International Classification of Diseases Tenth Revision (ICD-10) codes that featured hypertension (I10, I11, I12, I13, I15). Our selection of antihypertensive agents was limited to dihydropyridine calcium channel blockers (CCB) and angiotensin II receptor blockers (ARB), the most commonly prescribed antihypertensive agents (17, 18), to exclude the effects of adherence due to the class effect of antihypertensive medications. Therefore, all single and compound drugs of CCB or ARB sold

domestically from January 1, 2008 to December 31, 2013 were included according to the Anatomical Therapeutic Chemical (ATC) classification system of drugs (19). This totaled 108 types of drugs when classified according to the ATC system. Since the Korean release date of Exforge® (amlodipine/valsartan combination), the first ARB/CCB compound drug, was September 1, 2007, the analysis was started from 2008. Of the 167,793 patients taking targeted antihypertensive agents (ARB, CCB, ARB/CCB compound), only those aged 20 years or older were selected (N=167,234). To prevent statistical deviation because of extreme values, the upper 0.01% value for the number of drugs and diagnoses and missing values were excluded. Most ARB, CCB, and SPC of ARB/CCB are prescribed as a once-a-day dosing. When a high-dose prescription is needed in Korea, most clinicians prescribe one tablet high dose rather than two tablets regular dose, because of insurance coverage standards. Therefore, most antihypertensive agents are prescribed as a 0.5 tablet or 1 tablet once a day. Thus, we excluded prescriptions that were not 0.5 or 1 tablet once a day (N=162,564). In addition, only those who received antihypertensive medication for at least one year were selected to ensure a more objective and stable measurement of medication adherence. As a result, 116,677 patients were ultimately selected for the study (Figure 1). This study was approved by the institutional review board (IRB) at the Seoul National University Hospital (IRB No.E-15-5-079-673) and National Health Insurance review committee for research support (NHIS-2017-2-610). Written informed consent was waived.

Assessment of adherence

Medication adherence was calculated using the Medication Possession Ratio (MPR), a frequently used indirect measurement method (5, 7, 20). MPR is calculated by dividing the total days supplied (excluding supplied days for the last clinic visit) by the number of days between the first and last refills (7).

MPR = total days supplied (TDS)/number of days between the first and last refills (prescription period, [PP])

The limitation of MPR is that adherence can be overestimated, because the total days supplied is assumed to be the actual days the drug is used (20, 21). Nevertheless, MPR was used in this study, because it is considered the best method to evaluate the adherence of antihypertensive agents using retrospective data (21). Theoretically, MPR may exceed 100% if the patient visits prematurely before the drug is consumed. Thus, for the purposes of this study, MPR measuring over 100% was capped at 100%.

Factors related to adherence

Medication adherence is determined by the interactions of factors associated with the patient, condition, therapy, healthcare system, and social/economic status etc. (1, 5, 7, 10). In this study, factors associated with the patient (age, sex), condition (comorbidity), therapy (drug costs, number of concurrent drugs, prescription period), healthcare system (insurance coverage), and social/economic status (income,

residence) were derived as the confounding variables and used in the statistical analysis. Education, occupation, related symptoms, adverse effects of the treatment, family and caregiver status, and medical staff factors, which are known to affect adherence, were not included in the study, because they were not identifiable in the NHIS-NSC (Supplementary Figure 2). In this study, comorbidities were calculated as the mean number of subjects' diagnoses during the observation period. The number of drugs taken was calculated as the average number of medication taken by subjects during the observation period.

Statistical analysis

The study subjects were divided into four groups according to the type of antihypertensive drugs they were taking: the only ARB group, only CCB group, MPC group, and SPC group. The average adherence of the four groups was examined. Each group was assigned according to the last drug taken by the subjects to categorize them without overlapping (Supplementary Figure 3). The reason for dividing the group according to the last drug is that selecting last period of hypertension treatment enables to attain relatively stabilized medication adherence than choosing early period of hypertension treatment. Another reason is that if the group is divided according to the initial drug taken, the SPC group may not be selected at all. We compared the average adherence of the four groups before and after adjusting confounding factors using analysis of covariance (ANCOVA). A subgroup analysis, which compared the differences in adherence of each group

according to age group (20–49 years, 50–64 years, 65–74 years, and 75 years–) and number of medications, was conducted. We also compared the adherence difference between MPC and SPC therapies according to the combination of an old-age standard (65 years) and number of medications. Finally, a sensitivity analysis of age and the number of medications affecting differences in adherence was conducted. All analyses were conducted by using STATA version 14.0(Stata Corp., College Station, TX, USA) and P-values less than 0.05 were regarded as statistically significant.

Results

Baseline characteristics

Of the 116,677 subjects, 29,400 were in the only ARB group, 58,401 in the only CCB group, 10,458 in the MPC group, and 18,418 in the SPC group. Among all subjects, 47.3% were male and 52.7% female. Most subjects were aged in their 60s, followed by those in their 50s, 70s, and 40s. Subjects had an average of three to four diagnoses, and were taking an average number of four medications (three to four drugs were the most common, followed by four to five) (Table 1).

Adherence comparison

The crude mean (mean± standard deviation, [SD]) of MPR for each group was 81.0±23.9% in the only ARB group, 80.9±23.2% in the only CCB group, 85.3±19.6% in the MPC group, and 87.7±17.7% in the SPC group. The adjusted MPR was 81.6% (95% confidence interval, [CI] 81.3-81.9) in the only ARB group, 79.7% (95% CI 79.5-79.9) in the only CCB group, 87.2% (95% CI 86.7-87.7) in the MPC group, and 89.7% (95% CI 89.3-90.0%) in the SPC group. Regardless of the adjustment, medication adherence was higher in the combination therapy than monotherapy group, and adherence of the SPC was higher than that of the MPC when comparing combination therapy ($p<0.05$) (Table 2). The adherence difference between the SPC and MPC groups was more significant as age and the number of drugs taken increased. The adherence difference between the two groups started to increase

when the number of medications was at 5-6, and further widened when the number of drugs increased ($p<0.05$) (Table 2). The adherence difference between the MPC and monotherapy groups began to decrease when the number of medications was at 7-8 and there was simply no difference between them when the number of total drugs taken were nine or more. However the difference between the SPC and monotherapy groups remained high (Table 2, Figure 2).

Subgroup analysis

The number of medications and adherence was analyzed by dividing subjects into an elderly and non-elderly group (cut-off age: 65 years). Regardless of the elderly status, the adherence difference between the SPC and MPC groups increased when the number of drugs increased. The adherence difference started to increase significantly when the number of drugs taken was at 3–4 in the elderly group (aged 65 years and over) and 5–6 in the non-elderly group (aged 20–64 years) ($p<0.05$) (Figure 3). As a result of the sensitivity analysis based on the number of drugs per detailed age group (20–49 years, 50–64 years, 65–74 years, and 75 years–), the same tendency emerged for overall medication adherence. The 20–49 years age group and those aged more than 75 years, a relatively small number of samples, demonstrated a similar tendency, but were borderline significant (Table 3).

Discussion

First, among the 1,048,061 patients enrolled in the NHIS-NSC from 2008 to 2013, 206,739 were diagnosed with hypertension, a prevalence of 19.7%. This differs somewhat from the 23.7% prevalence of hypertension in Korea, as reported by the Korean Centers for Disease Control and Prevention in 2013 (22). The reason for this difference seems to be that some people do not visit the hospital, even when diagnosed with hypertension. In fact, according to the Korean National Health and Nutrition Examination Survey (KNHANES) in 2013, the hypertension unawareness rate in Korea is 38.5% and untreated rate 34.7% (22). Considering these values, the prevalence of hypertension in the sample of this study is similar to the prevalence in Korea. Thus, the data used in this study can be considered a representative sample reflecting the characteristics of the whole population without bias. Comparing these rates with other countries, the unawareness and untreated rates of hypertension for 2007–2010 in the United States were 18.9% and 26% respectively (23). In England in 2006, the unawareness rate was 34.7% and untreated rate 48.7% (24). In Canada, the unawareness rate was 16.7% and untreated rate 20.1 % in the period 2007–2009 (24). These statistics indicate that the prevalence of hypertension identified in hospital is slightly lower than the overall prevalence, suggesting the same tendency as that found in this study.

In this study, the comparison of medication adherence of the four groups showed that adherence in combination therapy was higher than that for monotherapy. These results can be explained by applying the Health Belief Model (25, 26). Those who think that the severity of their hypertension is higher (e.g., by being prescribed combination therapy), are more likely to try to maintain adequate blood pressure by

taking antihypertensive agents as prescribed (27, 28). Schulz et al. found that when prescribing antihypertensive agents such as angiotensin converting enzyme inhibitors, ARB, Beta blockers, and CCB with diuretics as SPC therapy, patients' non-persistent risk was 8.4% lower and the possibility of non-adherence 19.4% lower than when prescribing these drugs as monotherapy without diuretics (29). Patel el al. also reported that patients with SPC therapy including Hydrochlorothiazide (HCTZ) demonstrated higher adherence than those using HCTZ monotherapy (30). Patel's study did not include subjects' baseline blood pressure information, but assumed that the monotherapy group was in early stage hypertension (30). In addition, Van Wijik et al. reported that the group that had initiated hypertension treatment with combination therapy had higher drug persistence than the group that started with monotherapy. Furthermore, they assumed that the reason for the higher persistence for the combination therapy group was related to the severity of the disease (31). Another study by Hashmi et al. reported that the average adherence of hypertensive patients when treated with monotherapy was 79%, 87% when treated with two drugs, and 90% when treated with three or more drugs (32). They also suggested that these results might be related to patients' increased awareness, because of their hypertension severity. As such, patients treated with combination therapy may be more adherent, because they are more likely to take medication with greater awareness than people treated with a single agent, since their hypertension is more severe.

In this study, the medication adherence of the SPC group was higher than that of the MPC group, as in previous research (11-15). A meta-analysis by Gupta et al., which compared antihypertensive medication adherence between SPC and MPC

prescriptions, confirmed the significantly higher adherence of the SPC group than the MPC group in all three cohort studies and two trials. [Odds ratio: 1.21(95% CI: 1.03 to 1.43)] (12). Sherrill et al. also performed a meta-analysis of seven studies that compared adherence between two groups using MPR. All seven studies reported significantly higher adherence in the SPC than MPC group, regardless of experience of antihypertensive agents (13).

Furthermore, previous studies comparing medication adherence to an SPC and MPC of ARB/CCB regimen, such as this study, indicated the same results (14, 15). In a study using pharmacy claims data by Zeng et al., the proportion of good adherence in the ARB/CCB SPC group was 45.9%, higher than the 35.3% of the MPC group (14). However, their study had fewer subjects and shorter observation periods, and only included two types of ARB/CCB compound pills for the SPC group (14). A real-world study by Basner et al. reported that the adherence of the ARB/CCB SPC group was higher than the MPC group [Odds ratio: 1.38, 95% CI: (1.24, 1.53)] (15). However, although Basner's study was set in the real-world, like this one, the sample size was small, including only 3,259 subjects and short-term observation for two years. Regarding drug type, they included various types of ARB/CCB for the MPC group, but limited the SPC group's drug type to the valsartan/amlodipine compound (15). Compared to the two studies mentioned above, the current study may have confirmed the differences in adherence between SPC and MPC prescriptions by analyzing long-term adherence for all ARBs, CCBs, and ARB/CCB compounds available during the period of observation using more systematic and representative large-scale data.

In addition, this study revealed that the higher the age, the greater the difference in

adherence between the SPC and MPC groups (Table 2, Figure 2). According to Salas et al., cognitive impairment is a factor in decreasing adherence to antihypertensive medication in isolated patients (33). Moreover, according to Schwartz et al., the rate of drug use errors in patients aged more than 75 years was higher than those of patients younger than 75 years (34). Presumably, it would be more difficult for the elderly to take both drugs accurately without withdrawing when taking MPC, since the frequency of decline in both physical and cognitive functions is higher in older age (33, 35). In this regard, as the patient's age increases, prescribing SPC, which simplifies the complexity of the medication regimen, may be more beneficial in increasing adherence, because for MPC prescriptions, compliance is reduced even if only one of two drugs is omitted.

We also confirmed that the greater the number of drugs taken, the greater the difference in adherence between the SPC and MPC groups (Table 2, Figure 2). The reason for this tendency is that patients on MPC need to take two drugs separately; thus, additional medication increases the complexity to a greater extent than when an SPC is taken. Toh et al. reported that a complex medication regimen such as multiple doses per day and multiple medications was significantly associated with higher non-compliance and readmissions (36). In addition, Pasina et al. reported that for the elderly aged more than 65 years hospitalized in internal medicine wards, the greater the number of prescription drugs at discharge, the lower the medication adherence and understanding of the purpose of medication (37). Therefore, prescribing an SPC regimen would be one way to increase medication adherence, especially of patients taking a large number of medications.

Finally, comparing the adherence difference between the SPC and MPC groups

according to both age and number of medications, there was a dose-response relationship tendency in which the more the number of drugs, the more prominent the difference regardless of age. However, this tendency started to be significant when number of drugs taking was three or more in the elderly group (aged 65 years and over) and five or more in the non-elderly group (aged 20–64 years) (Figure 3). Thus, the number of drugs affecting medication complexity showed a slight difference between the elderly and non-elderly group. The significant point of the number of medications, namely the significant point when the adherence difference between SPC and MPC becomes statistically significant, was slightly different between the detailed age groups, but the tendency remained the same (Table 3). The reason for this difference is that it is more difficult for older patients to adapt to regimen complexity, because of impaired physical and cognitive functions mentioned above (33, 35).

Our study is meaningful for two reasons. First, we analyzed the adherence of antihypertensive agents by using a sample of national cohort data samples that represents about 2.2% of the total population. Second, we analyzed the differences in medication adherence using cohort subjects who continued to take antihypertensive medication for at least one year for the maximum of six observed years. Although previous research analyzed medication adherence between the SPC and MPC of antihypertensive agents, (11-15) they were either short-term studies or analyzed in certain centers or under limited conditions. In addition, this study is meaningful, because it compared not only adherence to a combination therapy regimen type, but also compared it to monotherapy. Furthermore, we investigated the all prescription cases and average number of associated diseases,

which enabled us to more objectively adjust the factors associated with therapy and the condition.

On the other hand, this study did not reflect diverse socioeconomic factors such as education level and occupation, because of data limitations, and did not include specific factors such as caregiver status, the family environment, and healthcare provider factors. We also did not include antihypertensive agents other than ARB and CCB (e.g., diuretics, beta blockers, etc.) in the analysis. However, since the same class of drugs is homogenous, we were able to focus on comparing the adherence between SPC and MPC by eliminating the effects of drug class other than ARB and CCB, which affects adherence. Last, there is a weakness regarding adjusting for patients' comorbidities in the analysis. This study did not specify comorbidities according to severity, and only adjusted with the average number of diagnoses of the subject during the observation period. In fact, some patients are diagnosed with many mild diseases, while others have few diagnoses but more severe diseases. It is expected that further analysis that considers these factors will lead to more meaningful results in the near future.

In conclusion, those taking antihypertensive drugs as a combination therapy demonstrated higher adherence than those taking them as a monotherapy. Among the combination therapy patients, those on the SPC regimen demonstrated higher adherence than those taking the MPC prescription. This tendency was more pronounced with increasing age and the number of drugs taken. Therefore, if patients are older or taking numerous medications, prescribing antihypertensive agents as a SPC regimen may help improve medication adherence.

Contributors: SJ Kim conceived and designed the study, acquired and analyzed the data, interpreted

the study findings, and drafted the manuscript. OD Kwon analyzed the data, interpreted the study findings. SW oh, CM Lee, and BL Cho critically reviewed the manuscript. HC Choi conceived and designed the study, supervised and directed the conduct of the study, interpreted the study findings, and critically revised the manuscript. All authors had full access to all of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no other meeting the criteria have been omitted. HC Choi is the guarantor.

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Data sharing: Data are from the National Health Insurance service (NHIS). Interested researchers can request access to the data from NHIS. The detailed information for data access of NHIS could be obtained from the NHIS website (www.nhis.or.kr).

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Table 1 Baseline characteristics (n=116,677)

	Only ARB group N(%) or mean±SD	Only CCB group N(%) or mean±SD	MPC group N(%) or mean±SD	SPC group N(%) or mean±SD
Total	29,400 (25.2%)	58,401 (50.0%)	10,458 (9.0%)	18,418 (15.8%)
Male(47.3%, n=55,210)	13,834	25,499	5,507	10,370
Female(52.7%, n=61,467)	15,566	32,902	4,951	8,048
Age (year)	59.3 ± 12.5	62.4 ± 12.2	61.1 ± 12.4	56.9 ± 12.3
20-29 (0.6%)	263	204	48	148
30-39 (4.2%)	1,426	1,695	417	1,362
40-49 (16.6%)	5,455	8,003	1,653	4,283
50-59 (26.4%)	8,259	14,621	2,681	5,212
60-69 (27.7%)	7,761	17,177	2,944	4,475
70-79 (19.0%)	4,997	12,604	2,138	2,412
>=80 (5.5%)	1,239	4,097	577	526
Income				
Low (33.8%)	9,396	20,277	3,646	6,063
Middle (25.6%)	7,304	15,081	2,647	4,868
High (40.6%)	12,700	23,043	4,165	7,487
Residence				
Metropolitan (46.1%)	13,711	26,482	4,771	8,874
City (44.1%)	12,878	25,946	4,670	7,913
Rural (9.8%)	2,811	5,973	1,017	1,631
Health insurance				
National Health Insurance (94.2%)	27,679	55,113	9,662	17,406
Medical aid (5.8%)	1,721	3,288	796	1,012
Average No. of diagnoses	3.6 ± 1.9	3.1 ± 1.8	3.6 ± 1.9	3.1 ± 1.7
Average No. of medications	4.1 ± 2.2	3.9 ± 2.0	4.9 ± 2.1	3.7 ± 2.0
Average cost of anti-hypertension drug (₩)	651 ± 185	413 ± 141	982 ± 316	824 ± 196
Prescription period (day)	1,174 ± 575	1,477 ± 603	1,164 ± 560	972 ± 412
Total days supplied (day)	954 ± 562	1,218 ± 629	1,000 ± 545	855 ± 407
Medication possession ratio (MPR)	81.0±23.9	80.9 ± 23.2	85.3 ± 19.6	87.7 ± 17.7

ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; SPC, single pill combination; MPC, multiple pill combination; SD, standard deviation

Table 2 Medication adherences according to age and numbers of medications

	Ony ARB group (n=29,400)		Only CCB group (n=58,401)		MPC group (n=10,458)		SPC group (n=18,418)		p value†	MPR Differences‡	p value§
	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)			
	81.0	81.6 (81.3-81.9)	80.9	79.7 (79.5-79.9)	85.3	87.2 (86.7-87.7)	87.7	89.7 (89.3-90.0)	<0.01	2.5	<0.01
Age group (n=116,677)											
20-49y (n=24,957)	77.6	77.9 (77.3-78.4)	77.4	76.1 (75.5-76.7)	83.1	84.9 (83.7-86.0)	83.7	85.1 (84.4-85.8)	<0.01	0.2	0.20
50-64y (n=46,085)	82.6	83.0 (82.6-83.4)	82.9	81.9 (81.5-82.2)	86.4	88.0 (87.2-88.8)	89.3	90.8 (90.3-91.4)	<0.01	2.8	<0.01
65-74y (n=30,652)	82.4	83.0 (82.5-83.5)	82.3	81.4 (81.0-81.8)	86.5	88.1 (87.1-89.0)	90.6	92.3 (91.5-93.0)	<0.01	4.2	<0.01
>=75y (n=14,983)	79.3	80.1 (79.3-81.0)	77.4	76.6 (76.0-77.1)	83.3	84.8 (83.3-86.3)	87.5	89.3 (88.0-90.7)	<0.01	4.5	<0.01
Average No. of medications											
No.=1-2 (n=19,523)	79.6	80.3 (79.6-80.9)	79.4	78.1 (77.4-78.7)	85.8	87.6 (85.2-90.0)	85.9	87.9 (87.0-88.9)	<0.01	0.3	0.68
No.=3-4 (n=48,388)	81.3	82.0 (81.6-82.5)	81.6	80.6 (80.2-80.9)	87.3	88.7 (87.9-89.4)	87.4	89.2 (88.7-89.8)	<0.01	0.6	0.99
No.=5-6 (n=30,105)	81.9	82.3 (81.9-82.8)	81.4	80.5 (80.1-80.9)	86.4	87.5 (86.7-88.4)	89.3	90.6 (89.9-91.3)	<0.01	3.1	<0.01
No.=7-9 (n=13,071)	81.4	81.6 (80.9-82.3)	80.4	78.9 (78.2-79.6)	82.8	85.3 (84.1-86.5)	88.8	90.9 (89.8-92.0)	<0.01	5.6	<0.01
No.≥9 (n=5,590)	78.3	77.9 (76.8-79.0)	78.3	76.3 (75.2-77.4)	78.3	82.5 (80.6-84.4)	88.8	91.2 (89.3-93.1)	<0.01	8.7	<0.01

ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; SPC, single pill combination; MPC, multiple pill combination; MPR, Medication possession ratio; CI, confidence interval

* Adjusted for factors associated with the patient (age, sex), condition (comorbidity), therapy (drug costs, number of concurrent drugs, prescription period), the healthcare system (insurance coverage), and the social/economic status (income, residence)

† p value of crude MPR mean

‡ MPR differences = adjusted MPR of SPC group – adjusted MPR of MPC group

§ p value of MPR differences.

Analyses were performed using ANCOVA

Table 3 Sensitivity analysis for medication adherences according to age and numbers of medications

	Ony ARB group (n=29,400)		Only CCB group (n=58,401)		MPC group (n=10,458)		SPC group (n=18,418)		p value†	MPR Differences‡	p value§
	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)			
20-49y (n=24,957)											
No.=1-2 (n=6,827)	76.7	76.6 (75.6-77.6)	75.8	74.7 (73.4-76.0)	82.3	84.1 (80.2-88.0)	83.4	84.8 (83.4-86.1)	<0.01	0.7	0.78
No.=3-4 (n=11,768)	78.2	78.5 (77.6-79.3)	78.6	77.5 (76.8-78.3)	85.6	86.7 (85.2-88.2)	83.9	85.1 (84.1-86.1)	<0.01	-1.6	0.01
No.=5-6 (n=4,595)	78.1	78.6 (77.4-79.8)	76.7	75.3 (74.0-76.6)	82.2	83.9 (81.6-86.3)	84.2	85.3 (83.5-87.0)	<0.01	1.3	0.70
No.=7-9 (n=1,360)	79.4	79.3 (76.9-81.2)	77.5	76.7 (74.1-79.4)	76.7	78.6 (74.5-82.7)	81.9	82.4 (79.0-85.8)	<0.01	3.8	0.13
No.≥9 (n=407)	68.7	67.1 (62.6-71.6)	72.4	68.0 (63.1-73.0)	73.2	81.4 (74.0-88.8)	86.5	89.8 (82.4-97.1)	<0.01	8.4	0.05
50-64y (n=46,085)											
No.=1-2 (n=7,933)	81.8	81.9 (81.0-82.9)	81.4	81.0 (80.1-81.9)	88.9	89.2 (85.6-92.9)	88.5	89.3 (87.8-90.7)	<0.01	0.1	0.45
No.=3-4 (n=20,396)	82.5	83.0 (82.4-83.6)	83.2	82.3 (81.9-82.8)	88.3	89.5 (88.3-90.6)	89.1	90.4 (89.6-91.2)	<0.01	0.9	0.72
No.=5-6 (n=11,657)	83.5	83.7 (83.0-84.4)	83.8	83.2 (82.6-83.9)	87.8	88.5 (87.3-89.8)	90.3	91.1 (90.0-92.1)	<0.01	2.5	<0.01
No.=7-9 (n=4,438)	83.4	83.4 (82.2-84.5)	82.5	80.4 (79.2-81.5)	81.9	85.1 (83.1-87.1)	89.9	92.3 (90.6-94.0)	<0.01	7.2	<0.01
No.≥9 (n=1,661)	79.2	78.8 (76.9-80.6)	81.5	78.7 (76.7-80.8)	78.2	83.4 (80.3-86.4)	89.6	91.3 (88.3-94.3)	<0.01	7.9	<0.01
65-74y (n=30,652)											
No.=1-2 (n=3,412)	81.3	82.5 (80.6-84.4)	81.1	80.3 (79.2-81.4)	88.8	91.1 (85.5-96.8)	88.9	91.0 (88.3-93.8)	<0.01	-0.1	0.94
No.=3-4 (n=11,308)	83.5	83.9 (83.0-84.8)	83.0	82.5 (81.9-83.1)	88.7	89.2 (87.5-90.9)	90.3	91.6 (90.3-92.9)	<0.01	2.4	0.03
No.=5-6 (n=9,267)	83.1	83.1 (82.3-84.0)	82.7	82.3 (81.6-83.0)	88.0	88.3 (86.8-89.8)	91.5	92.5 (91.2-93.8)	<0.01	4.2	<0.01
No.=7-9 (n=4,562)	81.3	81.7 (80.5-82.9)	81.7	80.4 (79.3-81.5)	85.4	87.4 (85.4-89.4)	90.8	92.5 (90.7-94.4)	<0.01	5.2	<0.01
No.≥9 (n=2,103)	79.8	79.3 (77.5-81.1)	79.1	77.1 (75.4-81.1)	78.6	83.1 (79.9-86.2)	90.2	92.5 (89.5-95.6)	<0.01	9.5	<0.01
>=75y (n=14,983)											
No.=1-2 (n=1,351)	80.6	81.0 (77.1-84.9)	75.7	75.5 (73.8-77.3)	82.4	83.1 (72.1-94.0)	85.4	85.9 (80.3-91.5)	<0.01	2.9	0.69
No.=3-4 (n=4,916)	79.2	80.4 (78.7-82.1)	78.5	77.9 (77.0-78.9)	85.2	85.6 (82.6-88.6)	87.4	88.8 (86.3-91.2)	<0.01	3.2	0.42
No.=5-6 (n=4,586)	79.8	80.5 (79.0-82.0)	77.4	76.5 (75.4-77.6)	83.4	85.2 (82.6-87.8)	88.7	90.4 (87.9-92.8)	<0.01	5.2	0.01
No.=7-9 (n=2,711)	79.3	79.6 (77.9-81.4)	76.8	75.8 (74.3-77.2)	83.1	85.3 (82.3-88.2)	87.6	89.4 (86.4-92.3)	<0.01	4.1	0.18
No.≥9 (n=1,419)	77.8	77.4 (75.1-79.7)	75.5	74.9 (72.8-77.0)	80.2	81.3 (77.1-85.4)	85.7	88.6 (84.2-93.0)	<0.01	7.4	0.06

ARB,angiotensin II receptor blockers; CCB,calcium channel blockers; SPC,single pill combination; MPC,multiple pill combination; MPR, Medication possession ratio; CI, confidence interval

* Adjusted for factors associated with the patient (age, sex), condition (comorbidity), therapy (drug costs, number of concurrent drugs, prescription period), the healthcare system (insurance coverage), and the

social/economic status (income, residence)

† p value of crude MPR mean

‡ MPR differences = adjusted MPR of SPC group – adjusted MPR of MPC group

§ p value of MPR differences.

Analyses were performed using ANCOVA

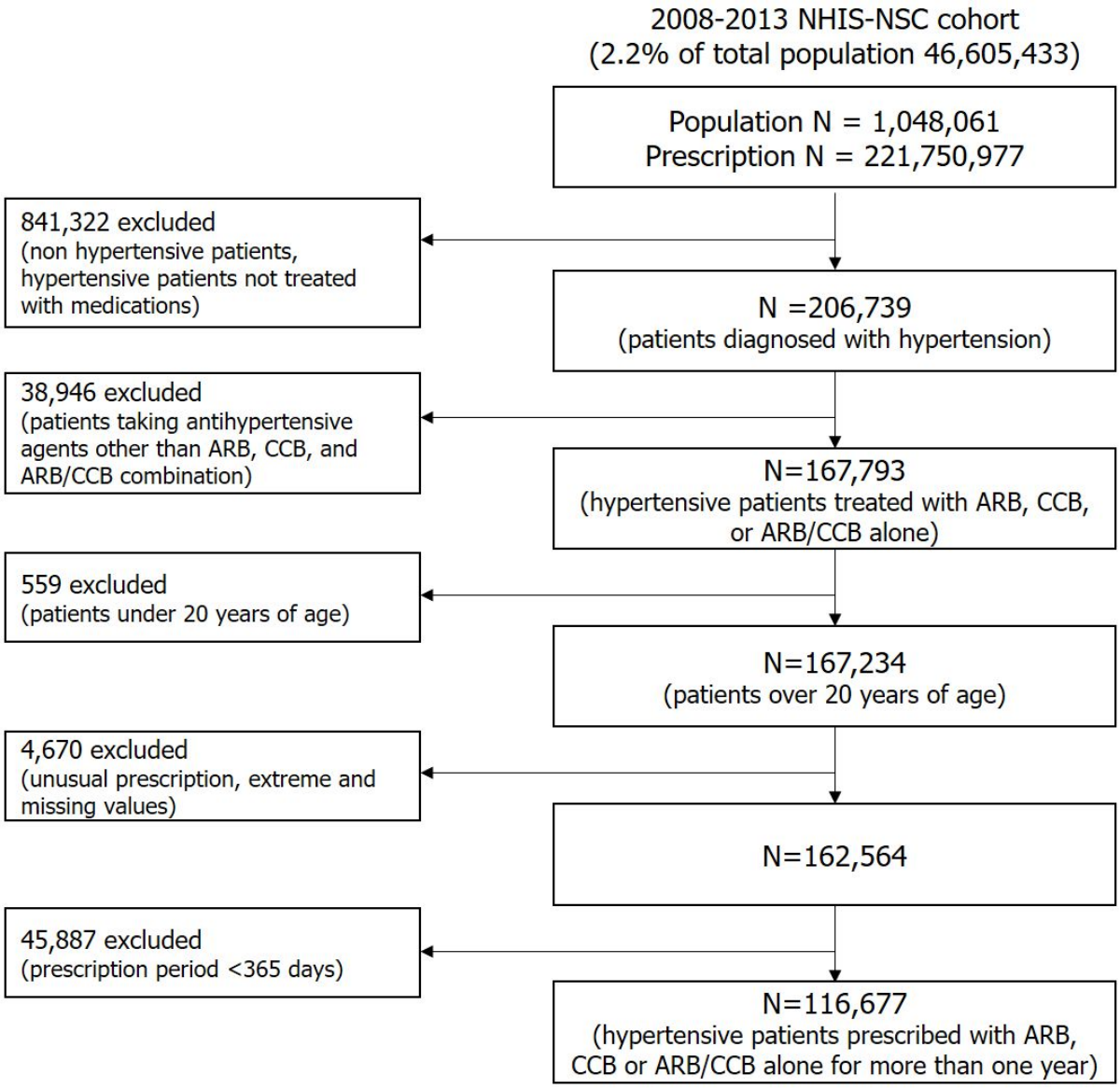
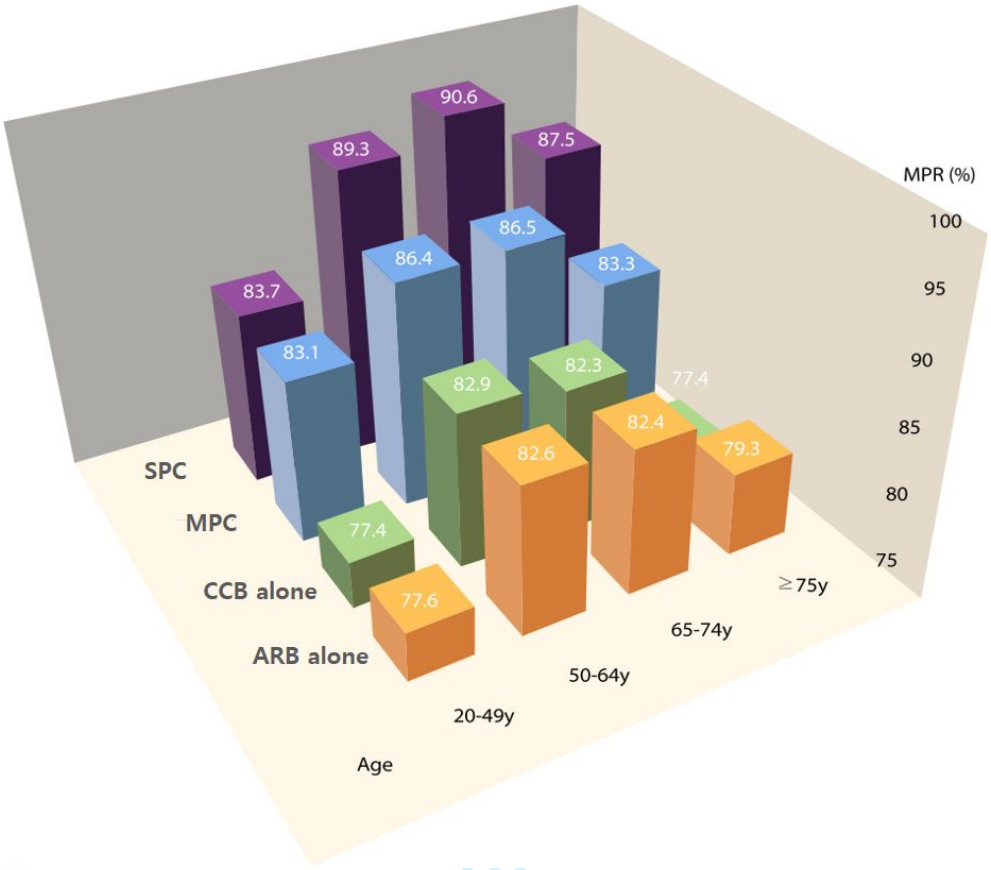
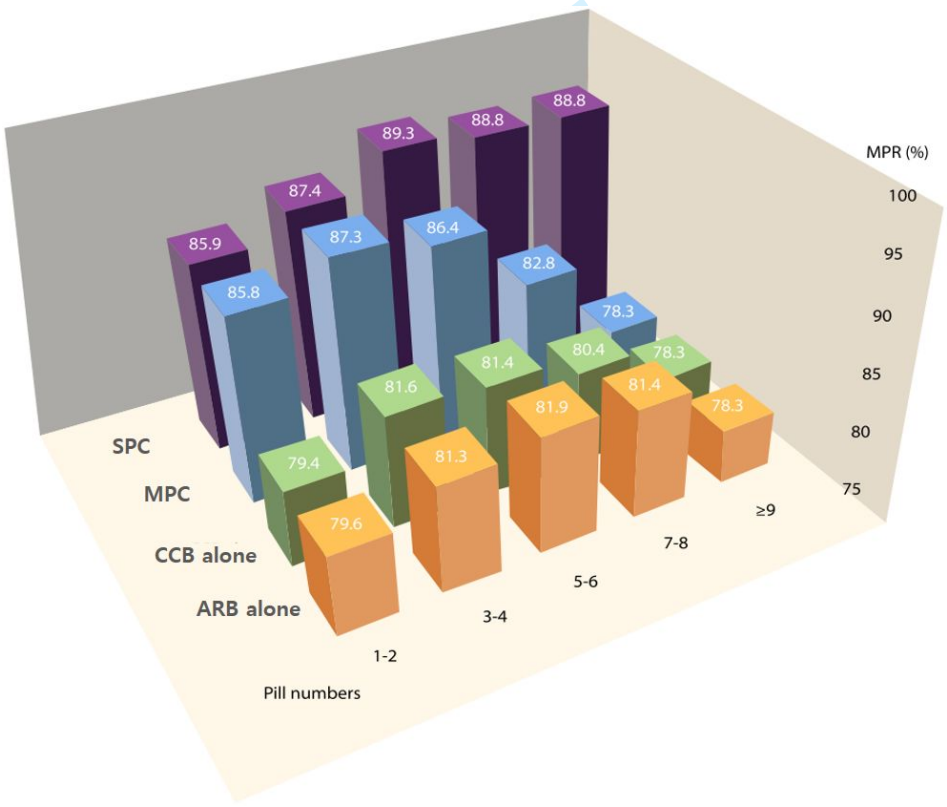


Figure 1 Study population and data collection

ARB (angiotensin II receptor blockers), CCB (calcium channel blockers), MPC (multiple pill combination), SPC (single pill combination)



Adherence change according to age group



Adherence change according to the number of medications

Figure 2 Trends of medication adherences according to age group and the number of medications

MPC (multiple pill combination), SPC (single pill combination), MPR (medication possession ratio), ARB (angiotensin II receptor blockers), CCB (calcium channel blockers)

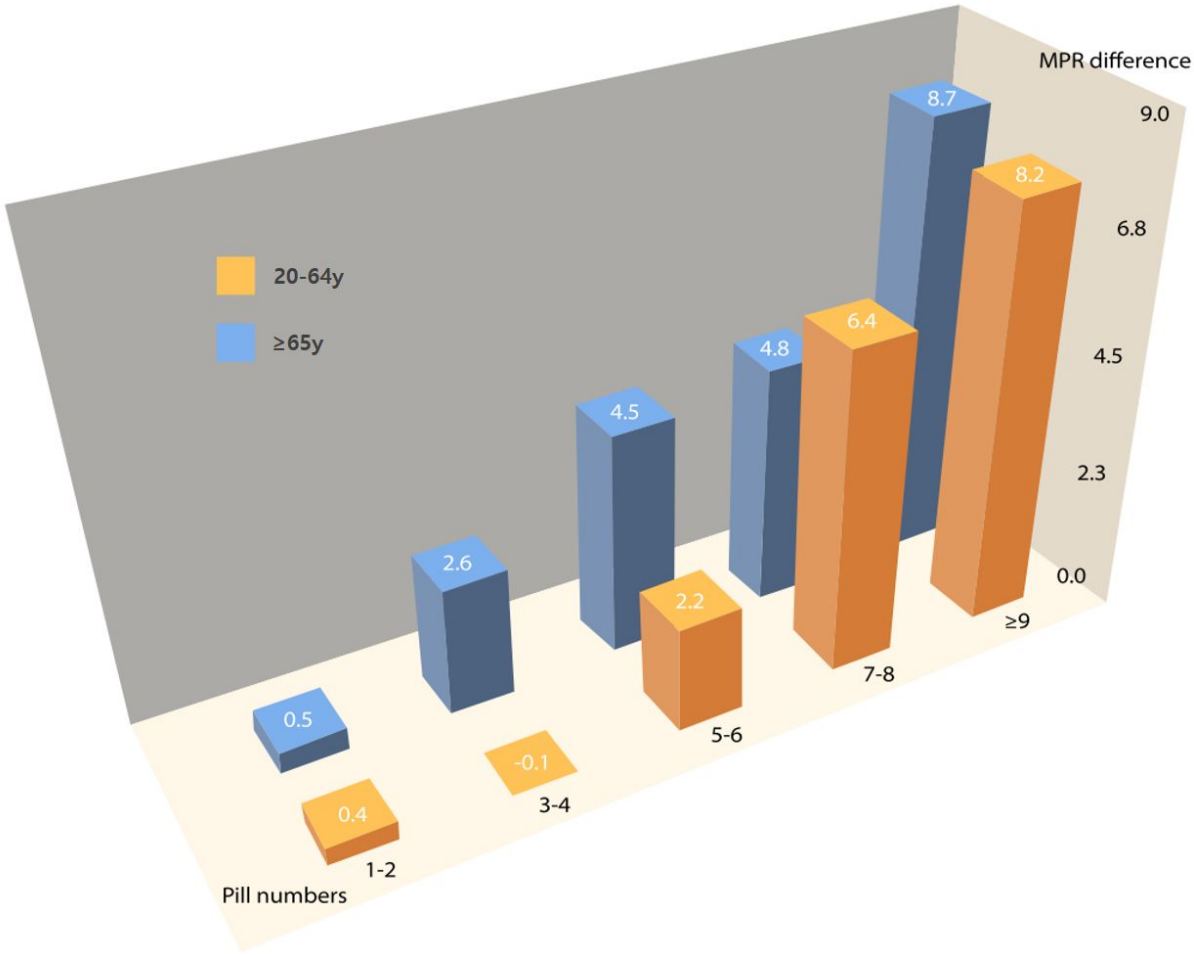


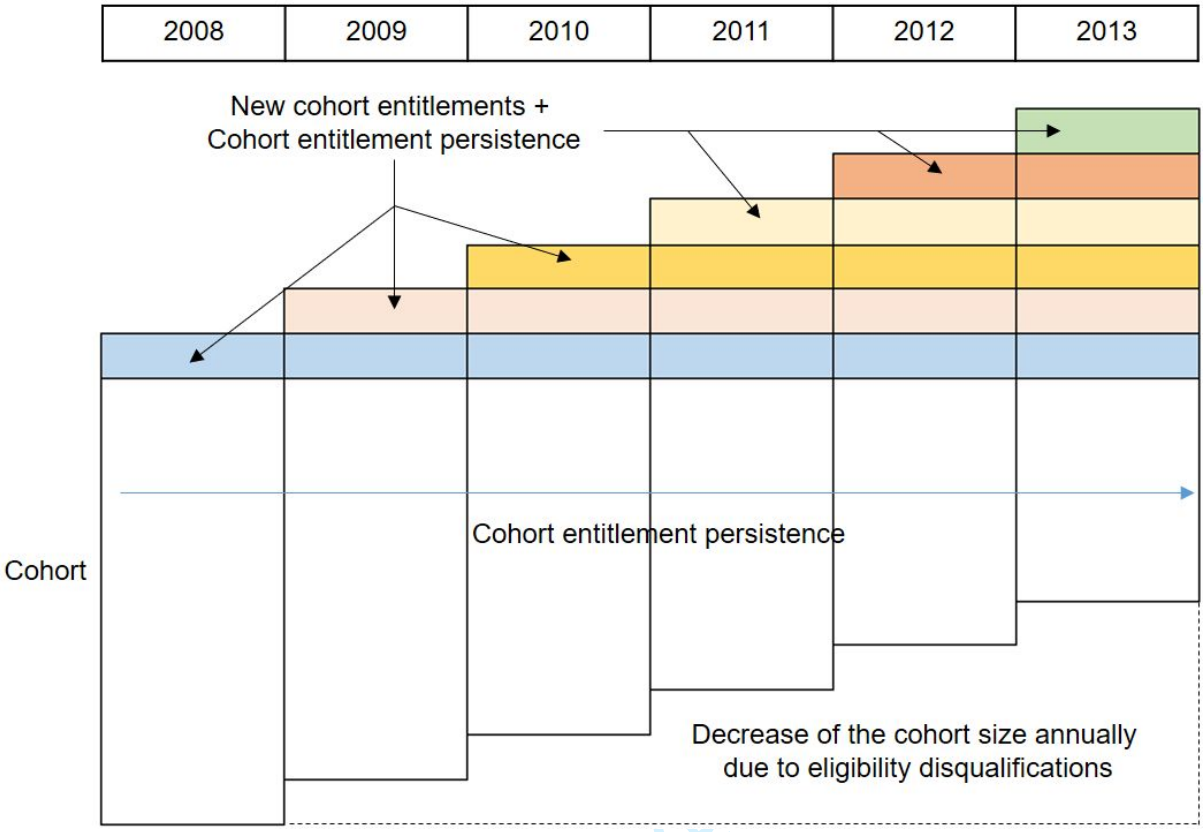
Figure 3 Difference of medication adherences between MPC and SPC therapies according to combinations of pill numbers and age

The number of drugs for which the adherence difference begins to increase is 3-4 in the elderly group (≥65year) and 5–6 in the non-elderly group (20–64year) ($p<0.05$).

MPC (multiple pill combination), SPC (single pill combination), MPR (medication possession ratio)

*MPR difference = MPR of SPC group – MPR of MPC group

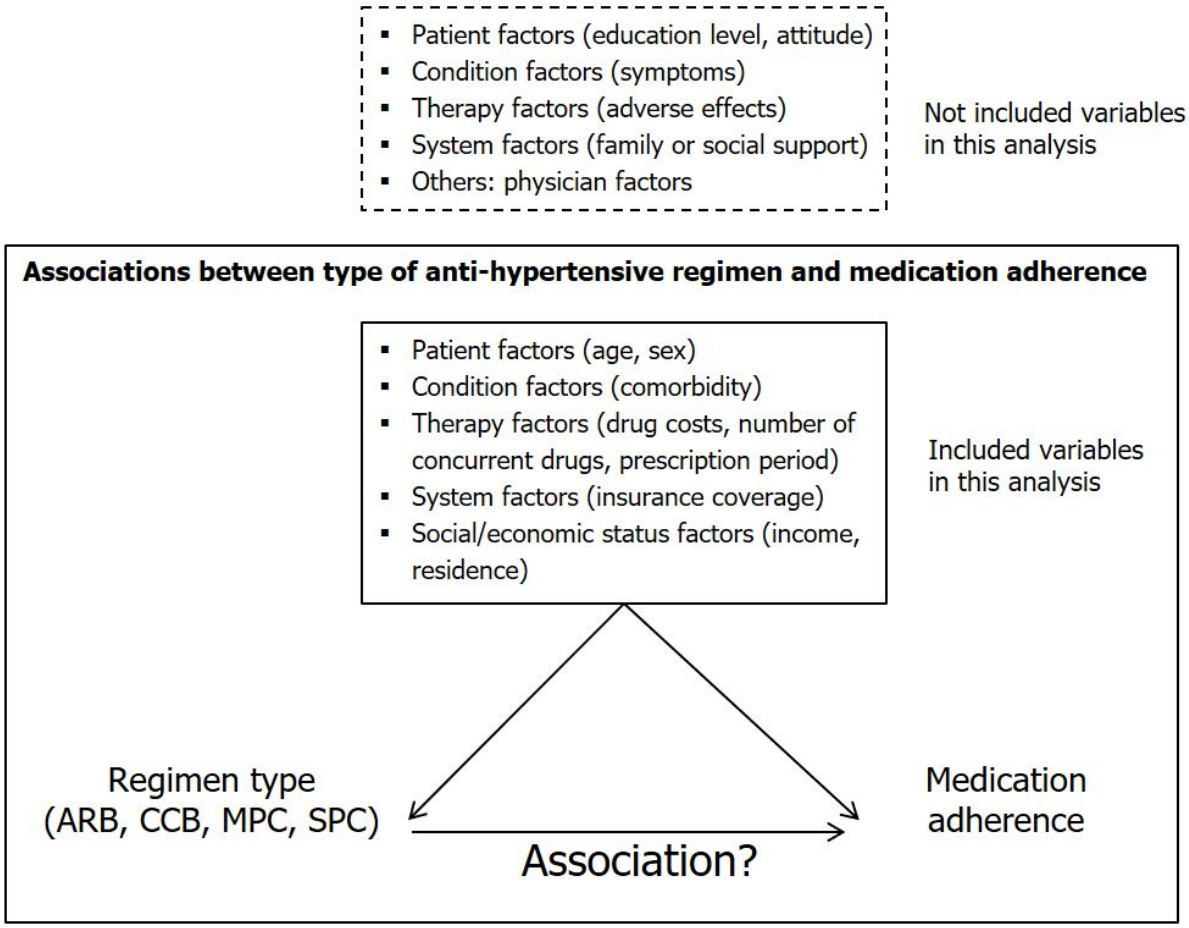
Supplementary online contents. A single pill combination of antihypertensives does improve adherence: A Korean nationwide study



Supplementary figure 1 Dynamic cohort design

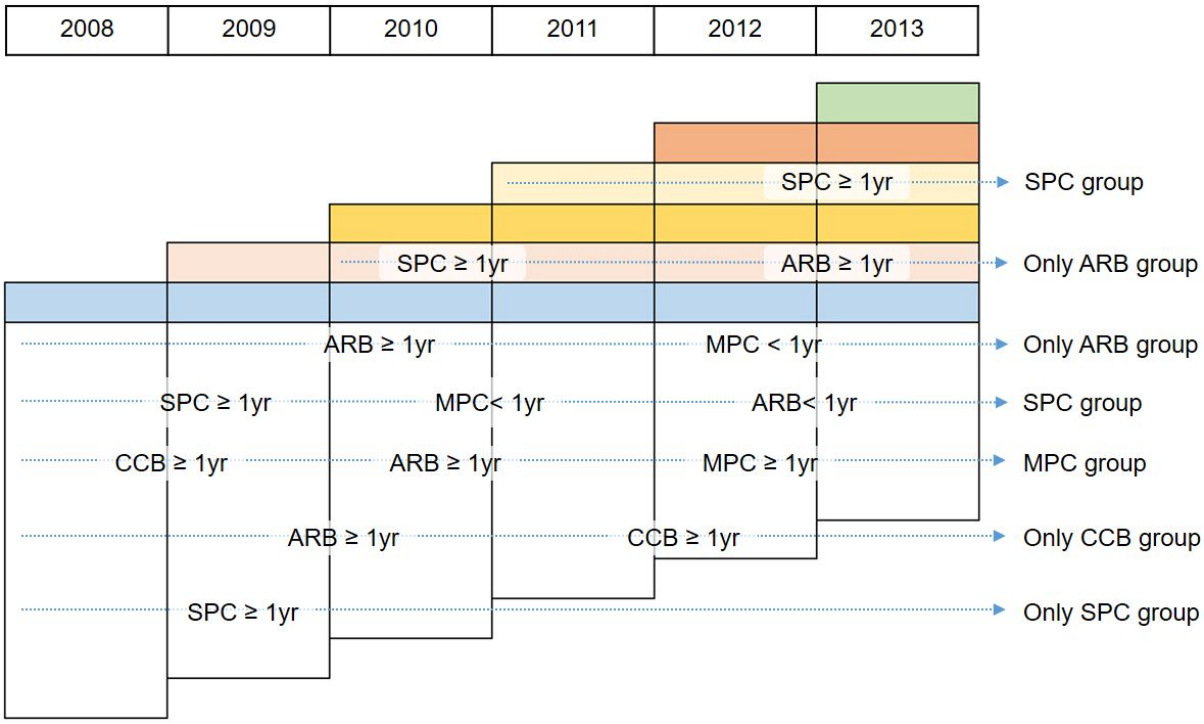
Cohort size: About one million/year (2.2% of total population)

Cohort data include qualification data (birth, death, sex, family relationship, address, property, income, insurance type) and medical service use data (billing statement, medical records, diagnosis record, prescription record, etc.)



Supplementary figure 2 Analysis scheme for factors related with anti-hypertensive medication adherence

ARB (angiotensin II receptor blockers), CCB (calcium channel blockers), MPC (multiple pill combination), SPC (single pill combination)



Supplementary figure 3 Classification definition of anti-hypertension medication groups

ARB (angiotensin II receptor blockers), CCB (calcium channel blockers), SPC (single pill combination), MPC (multiple pill combination)

STROBE Statement—checklist of items that should be included in reports of observational studies

Title and abstract	1.	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was found. **(mentioned in page 1-4 of the manuscript)**
Introduction		
Background/rationale	2.	Explain the scientific background and rationale for the investigation being reported. **(mentioned in page 5 of the manuscript)**
Objectives	3.	State specific objectives, including any prespecified hypotheses. **(mentioned in page 5-6 of the manuscript)**
Methods		
Study design	4.	Present key elements of study design early in the paper. **(mentioned in page 7-8 of the manuscript)**
Setting	5.	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow up, and data collection. **(mentioned in page 7-11 of the manuscript)**
Participants	6.	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(mentioned in page 7-11 of the manuscript)**
Variables	7.	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. **(mentioned in page 8-10 of the manuscript)**
Data source/measurement	8.	For each variable of interest, give sources of data and details of method of assessment (measurement). Describe comparability of assessment methods if there is more than one group. **(mentioned in page 7-11 of the manuscript)**
Bias	9.	Describe any efforts to address potential sources of bias. **(mentioned in page 7-11 of the manuscript)**
Study size	10.	Explain how the study size was arrived at.

		(mentioned in page 7-8 of the manuscript)
Quantitative variables	11.	Explain how quantitative variables were handled in the analyses. **(mentioned in page 7-9 of the manuscript)**
Statistical methods	12.	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. **(mentioned in page 9-11 of the manuscript)**
Results		
Participants	13.	(a) Report numbers of individuals at each stage study- eg, numbers of potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow up. And analysed. (b) Give reasons for non-participation at each age. (c) Consider use of a flow diagram. **(mentioned in page 12-13 of the manuscript)**
Descriptive data	14.	(a) Give characteristics of study participants (eg, demographic, clinical social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. **(mentioned in page 12 of the manuscript)**
Outcome data	15.	Report numbers of outcome events or summary measures over time. **(mentioned in page 12-13 of the manuscript)**
Main results	16.	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimated and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **(mentioned in page 12-13 of the manuscript)**
Other analyses	17.	Report other analyses done- eg, analyses of subgroup and interactions, and sensitivity analyses.

		(mentioned in page 13 of the manuscript)
Discussion		
Key results	18.	Summarise key results with reference to study objectives **(mentioned in page 14-19 of the manuscript)**
Limitations	19.	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(mentioned in page 19 of the manuscript)**
Interpretation	20.	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. **(mentioned in page 14-19 of the manuscript)**
Generalisability	21.	Discuss the generalisability (external validity) of the study results. **(mentioned in page 14-19 of the manuscript)**
Other infromation		
Funding	22.	Give the source of funding and the role of the finders for the present study and, if applicable, for the original study on which the present article is based. **(mentioned in page 20 of the manuscript)**

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Effects of combination drugs on antihypertensive medication adherence in a real-world setting: A Korean Nationwide Study

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[Title Page]

Effects of combination drugs on antihypertensive medication adherence in a real-world setting: A Korean Nationwide Study

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Abstract

Objectives: We tried to clarify, by using representative national data in a real-world setting, whether single pill combinations (SPCs) of antihypertensives actually improves medication adherence.

Design: A nationwide population-based study

Setting: We used a 2.2% cohort (N=1,048,061) of total population (N=46,605,433) that was randomly extracted by National Health Insurance of Korea from 2008 to 2013.

Participants: We included patients (N=116,677) who were prescribed with the same antihypertensive drugs for at least one year and divided them into groups of ARB (Angiotensin-II-receptor-blocker)-only, CCB (Calcium-channel-blocker)-only, multiple pill combinations (MPCs), and SPCs of ARB/CCB.

Primary outcome measures: Medication possession ratio (MPR), a frequently used indirect measurement method of medication adherence.

Results: Adjusted MPR was higher in combination therapy (89.7% in SPC, 87.2% in MPC) than monotherapy (81.6% in ARB, 79.7% in CCB), and MPR of SPC (89.7%, confidence interval, [CI] 89.3-90.0) was higher than MPR of MPC (87.2%, CI 86.7-87.7) ($p<0.05$). In subgroup analysis, adherences of SPC and MPC were 92.3% (CI 91.5-93.0) versus 88.1% (CI 87.1-89.0) in aged 65-74 years and 89.3% (CI 88.0-90.7) versus 84.8% (CI 83.3-92.0) in 75 years or older($p<0.05$). According to total pill numbers, adherences of SPC and MPC were 90.9% (CI 89.8-92.0) versus 85.3% (CI 84.1-86.5) in 7-8 pills and 91.2% (CI 89.3-93.1) versus 82.5% (CI 80.6-84.4) in 9 or more ($p<0.05$). The adherence difference between SPC and MPC started to increase

at 5-6 pills and at 50-64 years ($p<0.05$). When analyzed according to elderly status, the adherence difference started to increase at 3-4 pills in the elderly (65 years and older) and at 5–6 in the non-elderly group (20-64 years) ($p<0.05$). These difference all widened further with increasing age and the total medications.

Conclusion: SPC regimens demonstrated higher adherence than MPC, and this tendency is more pronounced with increasing age and total number of medications.

Keywords hypertension, medication adherence, angiotensin II receptor blocker, calcium channel blocker, single pill combination

Strengths and limitations of this study

- The strength of this study is that we not only compared the adherence between combination and monotherapy of antihypertensive medications but also the adherence of single pill combination (SPC) and multiple pill combination (MPC) regimens in a real-world setting by using National Health Insurance Service National Sample Cohort (NHIS-NSC), a representative large scale health insurance claims data of Korea accounting for 2.2% of the total population.
- Another strength of this study is that we analyzed the differences in medication adherence of subjects who continued to take antihypertensive drugs for at least one year for the maximum of six observed years.
- NHIS-NSC data does not provide detailed information regarding some specific factors that could affect the medication adherence, such as the patient's education level, occupation, caregiver status, the family environment, and healthcare provider factors.
- We did not specify comorbidities according to severity, and only adjusted with the average number of diagnoses of the subject during the observation period.

Introduction

Adherence to medication is an explanation of drug taking behavior, and refers to taking drugs in compliance with the time, dose, and frequency prescribed by the healthcare provider (1). The World Health Organization (WHO) defines medication non-adherence as a medically ill state, because low medication adherence causes the illness to progress and lowers the overall health outcome (1). Non-adherence may lead to various clinical risks. In many studies, low adherence is associated with higher mortality and hospitalization rates than higher adherence (2-4). Also, in terms of health economics, non-adherent patients use healthcare resources more than do adherent patients, and consequently the burden of social illness increases because of the increase in additional medical expenses (5-7). Non-adherence is observed more frequently for chronic than acute diseases, especially for hypertension, for which non-adherence is reported in 50–70% of the cases (1, 7-9).

Adherence to medication is determined by various aspects such as factors associated with the patient, condition, therapy, the healthcare system, and the social/economic status etc. (1, 5, 7, 10) Thus, to improve adherence a strategic approach to the specific cause is needed. Regarding these factors, there were some previous studies showing a relation between a lower number of medications taken by a patient and higher adherence in chronic diseases such as hypertension (11-15). This implies that selecting a single pill combination (SPC) prescription could increase adherence compared to a multiple pill combination (MPC) prescription (11-15). However, most of the previous research reported results obtained under certain

center conditions or were short-term studies of small samples, and systematic field surveys using real-world representative data were not common. Therefore, the aim of this study is to investigate the effect of SPC on the adherence to antihypertensive medication in a real-world setting. In order to do this, we first checked the overall medication prescription status of hypertensive patients and investigated the relation between multiple medication prescriptions, age, and medication adherence to antihypertensive agents.

Methods

Data source

The data used in this study was obtained from the National Health Insurance Service National Sample Cohort (NHIS-NSC) of Korea. This data is a sample of 1,048,061 individuals, around 2.2% of the total population (N=46,605,433), and provides national health information according to sex, age, and income. In addition, this cohort data is obtained through continuous observation every year, and includes qualification data (birth, death, sex, family relationship, address, property, income, insurance type), medical service use data (billing statement, medical record, diagnosis record, prescription record, etc.), and health examination data (Supplementary Figure 1) (16).

Study population

In total, 206,739 hypertensive patients taking antihypertensive medications were selected from the 2008 to 2013 NHIS-NSC (N=1,048,061, total outpatient prescriptions: 221,750,977 cases). Hypertensive patients were defined as all patients with the International Classification of Diseases Tenth Revision (ICD-10) codes that featured hypertension (I10, I11, I12, I13, I15). Our selection of antihypertensive agents was limited to dihydropyridine calcium channel blockers (CCBs) and angiotensin II receptor blockers (ARBs), the most commonly prescribed antihypertensive agents (17, 18). This was to exclude the effects of adherence due to the class effect of antihypertensive medications. Therefore, all ARBs, CCBs and ARB/CCB compound

drugs, as classified according to the Anatomical Therapeutic Chemical (ATC) classification system of drugs (19), that were sold domestically from January 1, 2008 to December 31, 2013 were included as antihypertensive medication.. A total of 108 types of drugs were identified under the ATC system. Since the Korean release date of Exforge® (amlodipine/valsartan combination), the first ARB/CCB compound drug, was September 1, 2007, the analysis period was set as starting from 2008. Of the 167,793 patients taking targeted antihypertensive agents (ARBs, CCBs, and ARB/CCB compounds), only those aged 20 years or older were selected (N=167,234). To prevent statistical deviation caused by extreme values, the upper 0.01% values for number of drugs and diagnoses, along with missing values were excluded. Most ARB, CCB, and SPC of ARB/CCB are prescribed as a once-a-day dosing. When a high-dose prescription is needed in Korea, most clinicians prescribe one high dose tablet rather than two regular dose tablets, because of insurance coverage standards. Therefore, most antihypertensive agents are prescribed so that patients are directed to take 0.5 or 1 tablet once a day. Thus, we excluded prescriptions that were not in the '0.5 or 1 tablet once a day' form (N=162,564). In addition, only those who received antihypertensive medication for at least one year were selected to ensure a more objective and stable measurement of medication adherence. As a result, 116,677 patients were ultimately selected for the study (Figure 1). This study was approved by the institutional review board (IRB) at the Seoul National University Hospital (IRB No.E-15-5-079-673) and National Health Insurance review committee for research support (NHIS-2017-2-610). Written informed consent was waived.

Assessment of adherence

Medication adherence was calculated using the Medication Possession Ratio (MPR), a frequently used indirect measurement method (5, 7, 20). MPR is calculated by dividing the total days supplied (excluding supplied days for the last clinic visit) by the number of days between the first and last refills (7).

MPR = total days supplied (TDS)/number of days between the first and last refills (prescription period, [PP])

The limitation of MPR is that adherence can be overestimated, because the total days supplied is assumed to be the days the drug is actually used (20, 21). Nevertheless, MPR was used in this study because it is considered the best method to evaluate the adherence of antihypertensive agents using retrospective data (21). Theoretically, MPR may exceed 100% if the patient visits prematurely before the drug is fully consumed. Thus, for the purposes of this study, MPR measuring over 100% was capped at 100%.

Factors related to adherence

Medication adherence is determined by the interactions of factors associated with the patient, condition, therapy, healthcare system, and social/economic status etc. (1, 5, 7, 10). In this study, factors associated with the patient (age, sex), condition (comorbidity), therapy (drug costs, number of concurrent drugs, prescription period),

healthcare system (insurance coverage), and social/economic status (income, residence) were derived as confounding variables and used in the statistical analysis. Education, occupation, related symptoms, adverse effects of the treatment, family and caregiver status, and medical staff factors, which are known to affect adherence, were not included in the study, because they were not identifiable in the NHIS-NSC data (Supplementary Figure 2). In this study, comorbidities were calculated as the mean number of the subjects' diagnoses during the observation period. The number of drugs taken was calculated as the average number of medication taken by subjects during the observation period.

Statistical analysis

The study subjects were divided into four groups according to the type of antihypertensive drugs they were taking: the ARB-only group, CCB-only group, MPC group, and SPC group. The average adherence of the four groups was examined. Each group was assigned according to the last drug taken by the subjects to categorize them without overlapping (Supplementary Figure 3). The reason for dividing the group according to the last drug taken is that selecting the last period of hypertension treatment enables to attain relatively stabilized medication adherence than choosing an early period of hypertension treatment. Another reason is that if the group is divided according to the initial drug taken, the SPC group may not be selected at all. We compared the average adherence of the four groups before and after adjusting confounding factors using analysis of covariance (ANCOVA). A

subgroup analysis, which compared the differences in adherence of each group according to age group (20–49 years, 50–64 years, 65–74 years, and 75 years–) and number of medications, was conducted. We also compared the adherence difference between MPC and SPC therapies according to the combination of an old-age standard (65 years) and number of medications. Finally, a sensitivity analysis of age and the number of medications affecting differences in adherence was conducted. All analyses were conducted by using STATA version 14.0(Stata Corp., College Station, TX, USA) and P-values less than 0.05 were regarded as statistically significant.

Patient and public involvement

There was no patient or public involvement in the development of this study.

Results

Baseline characteristics

Of the 116,677 subjects, 29,400 were in the ARB-only group, 58,401 in the CCB-only group, 10,458 in the MPC group, and 18,418 in the SPC group. Among all subjects, 47.3% were male and 52.7% female. Most subjects were aged in their 60s, followed by those in their 50s, 70s, and 40s. Subjects had an average of three to four diagnoses, and were taking an average number of four medications (three to four drugs were the most common, followed by four to five) (Table 1).

Adherence comparison

The crude mean (mean± standard deviation, [SD]) of MPR for each group was 81.0±23.9% in the ARB-only group, 80.9±23.2% in the CCB-only group, 85.3±19.6% in the MPC group, and 87.7±17.7% in the SPC group. The adjusted MPR was 81.6% (95% confidence interval, [CI] 81.3-81.9) in the ARB-only group, 79.7% (95% CI 79.5-79.9) in the CCB-only group, 87.2% (95% CI 86.7-87.7) in the MPC group, and 89.7% (95% CI 89.3-90.0%) in the SPC group. Regardless of the adjustment, medication adherence was higher in the combination therapy than monotherapy groups, and adherence of the SPC group was higher than that of the MPC group when comparing combination therapies ($p<0.05$) (Table 2). The adherence difference between the SPC and MPC groups was more significant as age and the number of drugs taken increased. The adherence difference between the two groups started to increase when the number of medications was at 5-6, and further widened when the number of drugs increased ($p<0.05$) (Table 2). The adherence difference

between the MPC and monotherapy groups began to decrease when the number of medications was at 7-8 and there was simply no difference between them when the number of total drugs taken were nine or more. However the difference between the SPC and monotherapy groups remained high (Table 2, Figure 2).

Subgroup analysis

The number of medications and adherence was analyzed by dividing subjects into elderly and non-elderly groups (cut-off age: 65 years). Regardless of the elderly status, the adherence difference between the SPC and MPC groups increased when the number of drugs increased. The adherence difference started to increase significantly when the number of drugs taken was at 3–4 in the elderly group (aged 65 years and over) and 5–6 in the non-elderly group (aged 20–64 years) ($p<0.05$) (Figure 3). When a sensitivity analysis was conducted based on the number of drugs per detailed age group (20–49 years, 50–64 years, 65–74 years, and 75 years or older), the same tendency emerged for overall medication adherence. The age 20–49 group and age 75 or older group, which consisted of a relatively small number of samples, demonstrated a similar tendency, but the tendency was only marginally significant (Table 3).

Discussion

First, among the 1,048,061 patients enrolled in the NHIS-NSC from 2008 to 2013, 206,739 were diagnosed with hypertension, a prevalence of 19.7%. This differs somewhat from the 23.7% prevalence of hypertension in Korea, as reported by the Korean Centers for Disease Control and Prevention in 2013 (22). The reason for this difference seems to be that some people do not get medical treatment even when diagnosed with hypertension. In fact, according to the Korean National Health and Nutrition Examination Survey (KNHANES) in 2013, the hypertension unawareness rate in Korea is 38.5%, and the untreated rate is 34.7% (22). Considering these values, the prevalence of hypertension in the sample of this study is similar to the prevalence in Korea. Thus, the data used in this study can be considered a representative sample reflecting the characteristics of the whole population without bias. Comparing these rates with other countries, the unawareness and untreated rates of hypertension in the United States during 2007-2010 were 18.9% and 26%, respectively (23). In England in 2006, the unawareness rate was 34.7% and untreated rate 48.7% (24). In Canada, the unawareness rate was 16.7% and untreated rate 20.1 % in the period 2007–2009 (24). These statistics indicate that the prevalence of hypertension identified in hospitals is slightly lower than the overall prevalence, suggesting the same tendency as found in this study.

In this study, the comparison of medication adherence of the four groups showed that adherence in combination therapy was higher than that in monotherapy. These results can be explained by applying the Health Belief Model (25, 26). Those who think that the severity of their hypertension is higher (e.g., by being prescribed combination therapy), are more likely to try to maintain adequate blood pressure by

taking antihypertensive agents as prescribed (27, 28). Schulz et al. found that when prescribing antihypertensive agents such as angiotensin converting enzyme inhibitors, ARBs, Beta blockers, and CCBs with diuretics as SPC therapy, patients' non-persistent risk was 8.4% lower and the possibility of non-adherence 19.4% lower than when prescribing these drugs as monotherapy without diuretics (29). Patel el al. also reported that patients with SPC therapy including Hydrochlorothiazide (HCTZ) demonstrated higher adherence than those using HCTZ monotherapy (30). Patel's study did not include subjects' baseline blood pressure information, but assumed that the monotherapy group was in the early stage of hypertension (30). In addition, Van Wijik et al. reported that the group that had initiated hypertension treatment with combination therapy had higher drug persistence than the group that started with monotherapy. Furthermore, they assumed that the reason for the higher persistence for the combination therapy group was related to the severity of the disease (31). Another study by Hashmi et al. reported that the average adherence of hypertensive patients was 79% when treated with monotherapy, 87% when treated with two drugs, and 90% when treated with three or more drugs (32). They also suggested that these results might be related to patients' increased awareness, because of their hypertension severity. As such, patients treated with combination therapy may be more adherent, because they are more likely to take medication with greater awareness than people treated with a single agent since their hypertension is more severe.

In this study, the medication adherence of the SPC group was found to be higher than that of the MPC group, consistent with the findings of previous research (11-15). A meta-analysis by Gupta et al., which compared antihypertensive medication

adherence between SPC and MPC prescriptions, confirmed the significantly higher adherence of the SPC group than the MPC group in all three cohort studies and two trials. [Odds ratio: 1.21(95% CI: 1.03 to 1.43)] (12). Sherrill et al. also performed a meta-analysis of seven studies that compared adherence between two groups using MPR. All seven studies reported significantly higher adherence in the SPC than MPC group, regardless of experience of antihypertensive agents (13).

Furthermore, previous studies comparing medication adherence to SPC and MPC of ARB/CCB regimens, such as this study, indicated the same results (14, 15). In a study using pharmacy claims data by Zeng et al., the proportion of good adherence in the ARB/CCB SPC group was 45.9%, higher than the 35.3% of the MPC group (14). However, their study had fewer subjects and shorter observation periods, and only included two types of ARB/CCB compound pills for the SPC group (14). A real-world study by Basner et al. reported that the adherence of the ARB/CCB SPC group was higher than the MPC group [Odds ratio: 1.38, 95% CI: (1.24, 1.53)] (15). However, although Basner's study was set in the real-world like this study, the sample size was small, including only 3,259 subjects and short-term observation for two years. Regarding drug type, they included various types of ARB/CCB for the MPC group, but limited the SPC group's drug type to the valsartan/amlodipine compound (15). Compared to the two studies mentioned above, the current study may have confirmed the differences in adherence between SPC and MPC prescriptions by analyzing long-term adherence for all ARBs, CCBs, and ARB/CCB compounds available during the period of observation using a more systematic and representative large-scale data.

In addition, this study revealed that the higher the age, the greater the difference in

adherence between the SPC and MPC groups (Table 2, Figure 2). According to Salas et al., cognitive impairment is a factor in decreasing adherence to antihypertensive medication in isolated patients (33). Moreover, according to Schwartz et al., the rate of drug use errors in patients aged more than 75 years was higher than those of patients younger than 75 years (34). Presumably, it would be more difficult for the elderly to take both drugs accurately without omission when taking MPC medications, since the frequency of decline in both physical and cognitive functions is higher in older age (33, 35). In this regard, as the patient's age increases, prescribing SPCs that simplifies the complexity of the medication regimen may be more beneficial in increasing adherence, because for MPC prescriptions compliance is reduced even when only one of the prescribed drugs is omitted.

We also confirmed that the greater the number of drugs taken, the greater the difference in adherence between the SPC and MPC groups (Table 2, Figure 2). The reason for this tendency is that patients on MPC therapy need to take two drugs separately; the additional medication increases the complexity to a greater extent than when SPC medication is taken. Toh et al. reported that a complex medication regimen such as multiple doses per day and multiple medications was significantly associated with higher non-compliance and readmissions (36). In addition, Pasina et al. reported that for the elderly aged more than 65 years hospitalized in internal medicine wards, the greater the number of prescription drugs at discharge, the lower the medication adherence and understanding of the purpose of medication (37). Therefore, prescribing an SPC regimen would be one way to increase medication adherence, especially of patients taking a large number of medications.

Finally, comparing the adherence difference between the SPC and MPC groups

according to both age and number of medications, there was a dose-response relationship tendency in which the more the number of drugs, the more prominent the difference regardless of age. However, this tendency started to be significant when number of drugs taking was three or more in the elderly group (aged 65 years and over) and five or more in the non-elderly group (aged 20–64 years) (Figure 3). Thus, the number of drugs affecting medication complexity showed a slight difference between the elderly and non-elderly group. The significant point of the number of medications, namely the significant point when the adherence difference between SPC and MPC becomes statistically significant, was slightly different between the detailed age groups, but the tendency remained the same (Table 3). The reason for this difference is that it is more difficult for older patients to adapt to regimen complexity, because of impaired physical and cognitive functions mentioned above (33, 35).

Our study is meaningful for two reasons. First, we analyzed the adherence of antihypertensive agents by using a sample of national cohort data that represents about 2.2% of the total population. Second, we analyzed the differences in medication adherence using cohort subjects who continued to take antihypertensive medication for at least one year for the maximum of six observed years. Although previous research analyzed medication adherence between the SPC and MPC of antihypertensive agents, (11-15) they were either short-term studies or analyzed in certain centers or under limited conditions. In addition, this study is meaningful, because it compared not only adherence to a combination therapy regimen type, but also compared it to monotherapy. Furthermore, we investigated all of the prescriptions and the average number of associated diseases involved with the

patients, which enabled us to more objectively adjust the factors associated with the therapy and the patients' condition.

On the other hand, because of limitations in data, this study did not reflect diverse socioeconomic factors such as the patients' education level and occupation, and did not include specific factors such as caregiver status, the family environment, and healthcare provider factors. We also did not include antihypertensive agents other than ARBs and CCBs (e.g., diuretics, beta blockers, etc.) in the analysis. However, since the same class of drugs is homogenous, we were able to focus on comparing the adherence between SPC and MPC by eliminating the effects on adherence of drug classes other than ARBs and CCBs.

Moreover, there is a weakness in the analysis regarding adjusting for patients' comorbidities. This study did not specify comorbidities according to severity, and only adjusted with the average number of diagnoses of the subject during the observation period. But in reality, some patients are diagnosed with many mild diseases, while others have few diagnoses but more severe diseases. Also, while new diseases can be additionally diagnosed at any point in the observation period, a new disease diagnosed at a certain point cannot be considered as having affected the medication adherence of the whole observation period. That is why we adjusted the comorbidities as the average number of diagnoses.

Finally, due to the inevitable limitation of real-world claims data, we could not compare the first year adherence of each group even though the first year is usually an important phase for adherence in newly treated patients. When using real-world data such as the NHIS-NSC used here, it is practically impossible to divide subjects into certain drug groups without implementing some operationalization. This is due to

the fact that medications prescribed to patients can be changed, added or even discontinued during the course of the observation period. Moreover, we concluded that categorizing patients into four groups according to the last drug taken by subjects was the most ideal way since not many patients start with SPC as initial therapy unless their hypertension is severe. We also thought that comparing average adherence up to maximum of six years was suitable, since the subjects in our study were not limited to newly treated patients.

In conclusion, those taking antihypertensive drugs as a combination therapy demonstrated higher adherence than those taking them as a monotherapy. Among the combination therapy patients, those on the SPC regimen demonstrated higher adherence than those taking the MPC prescription. This tendency was more pronounced with increasing age and the number of drugs taken. Therefore, if patients are older or taking numerous medications, prescribing antihypertensive agents as a SPC regimen may help improve medication adherence.

Contributors: SJ Kim conceived and designed the study, acquired and analyzed the data, interpreted the study findings, and drafted the manuscript. OD Kwon analyzed the data, interpreted the study findings. SW oh, CM Lee, and BL Cho critically reviewed the manuscript. HC Choi conceived and designed the study, supervised and directed the conduct of the study, interpreted the study findings, and critically revised the manuscript. All authors had full access to all of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no other meeting the criteria have been omitted. HC Choi is the guarantor.

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Data sharing: Data are from the National Health Insurance service (NHIS). Interested researchers can request access to the data from NHIS. The detailed information for data access of NHIS could be obtained from the NHIS website (www.nhis.or.kr).

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Table 1 Baseline characteristics (n=116,677)

	ARB-only group N(%) or mean±SD	CCB-only group N(%) or mean±SD	MPC group N(%) or mean±SD	SPC group N(%) or mean±SD	p value
Total	29,400 (25.2%)	58,401 (50.0%)	10,458 (9.0%)	18,418 (15.8%)	
Male(47.3%, n=55,210)	13,834	25,499	5,507	10,370	<0.01
Female(52.7%, n=61,467)	15,566	32,902	4,951	8,048	
Age (year)	59.3 ± 12.5	62.4 ± 12.2	61.1 ± 12.4	56.9 ± 12.3	<0.01
20-29 (0.6%)	263	204	48	148	
30-39 (4.2%)	1,426	1,695	417	1,362	
40-49 (16.6%)	5,455	8,003	1,653	4,283	
50-59 (26.4%)	8,259	14,621	2,681	5,212	
60-69 (27.7%)	7,761	17,177	2,944	4,475	
70-79 (19.0%)	4,997	12,604	2,138	2,412	
>=80 (5.5%)	1,239	4,097	577	526	
Income					<0.01
Low (33.8%)	9,396	20,277	3,646	6,063	
Middle (25.6%)	7,304	15,081	2,647	4,868	
High (40.6%)	12,700	23,043	4,165	7,487	
Residence					<0.01
Metropolitan (46.1%)	13,711	26,482	4,771	8,874	
City (44.1%)	12,878	25,946	4,670	7,913	
Rural (9.8%)	2,811	5,973	1,017	1,631	
Health insurance					<0.01
National Health Insurance (94.2%)	27,679	55,113	9,662	17,406	
Medical aid (5.8%)	1,721	3,288	796	1,012	
Average No. of diagnoses	3.6 ± 1.9	3.1 ± 1.8	3.6 ± 1.9	3.1 ± 1.7	<0.01
Average No. of medications	4.1 ± 2.2	3.9 ± 2.0	4.9 ± 2.1	3.7 ± 2.0	<0.01
Average cost of anti-hypertension drug (₩)	651 ± 185	413 ± 141	982 ± 316	824 ± 196	<0.01
Prescription period (day)	1,174 ± 575	1,477 ± 603	1,164 ± 560	972 ± 412	<0.01
Total days supplied (day)	954 ± 562	1,218 ± 629	1,000 ± 545	855 ± 407	<0.01
Medication possession ratio (MPR)	81.0±23.9	80.9 ± 23.2	85.3 ± 19.6	87.7 ± 17.7	<0.01

ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; SPC, single pill combination; MPC, multiple pill combination; SD, standard deviation

Table 2 Medication adherences according to age and numbers of medications

	ARB-only group (n=29,400)		CCB-only group (n=58,401)		MPC group (n=10,458)		SPC group (n=18,418)		p value†	MPR Differences‡	p value§
	Crude MPR mean	Adjusted MPR mean*(95%CI)	Crude MPR mean	Adjusted MPR mean*(95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)			
	81.0	81.6 (81.3-81.9)	80.9	79.7 (79.5-79.9)	85.3	87.2 (86.7-87.7)	87.7	89.7 (89.3-90.0)	<0.01	2.5	<0.01
Age group (n=116,677)											
20-49y (n=24,957)	77.6	77.9 (77.3-78.4)	77.4	76.1 (75.5-76.7)	83.1	84.9 (83.7-86.0)	83.7	85.1 (84.4-85.8)	<0.01	0.2	0.20
50-64y (n=46,085)	82.6	83.0 (82.6-83.4)	82.9	81.9 (81.5-82.2)	86.4	88.0 (87.2-88.8)	89.3	90.8 (90.3-91.4)	<0.01	2.8	<0.01
65-74y (n=30,652)	82.4	83.0 (82.5-83.5)	82.3	81.4 (81.0-81.8)	86.5	88.1 (87.1-89.0)	90.6	92.3 (91.5-93.0)	<0.01	4.2	<0.01
>=75y (n=14,983)	79.3	80.1 (79.3-81.0)	77.4	76.6 (76.0-77.1)	83.3	84.8 (83.3-86.3)	87.5	89.3 (88.0-90.7)	<0.01	4.5	<0.01
Average No. of medications											
No.=1-2 (n=19,523)	79.6	80.3 (79.6-80.9)	79.4	78.1 (77.4-78.7)	85.8	87.6 (85.2-90.0)	85.9	87.9 (87.0-88.9)	<0.01	0.3	0.68
No.=3-4 (n=48,388)	81.3	82.0 (81.6-82.5)	81.6	80.6 (80.2-80.9)	87.3	88.7 (87.9-89.4)	87.4	89.2 (88.7-89.8)	<0.01	0.6	0.99
No.=5-6 (n=30,105)	81.9	82.3 (81.9-82.8)	81.4	80.5 (80.1-80.9)	86.4	87.5 (86.7-88.4)	89.3	90.6 (89.9-91.3)	<0.01	3.1	<0.01
No.=7-9 (n=13,071)	81.4	81.6 (80.9-82.3)	80.4	78.9 (78.2-79.6)	82.8	85.3 (84.1-86.5)	88.8	90.9 (89.8-92.0)	<0.01	5.6	<0.01
No.≥9 (n=5,590)	78.3	77.9 (76.8-79.0)	78.3	76.3 (75.2-77.4)	78.3	82.5 (80.6-84.4)	88.8	91.2 (89.3-93.1)	<0.01	8.7	<0.01

ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; SPC, single pill combination; MPC, multiple pill combination; MPR, Medication possession ratio; CI, confidence interval

* Adjusted for factors associated with the patient (age, sex), condition (comorbidity), therapy (drug costs, number of concurrent drugs, prescription period), the healthcare system (insurance coverage), and the social/economic status (income, residence)

† p value of crude MPR mean

‡ MPR differences = adjusted MPR of SPC group – adjusted MPR of MPC group

§ p value of MPR differences.

Analyses were performed using ANCOVA

Table 3 Sensitivity analysis for medication adherences according to age and numbers of medications

	ARB-only group (n=29,400)		CCB-only group (n=58,401)		MPC group (n=10,458)		SPC group (n=18,418)		p value†	MPR Differences‡	p value§
	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)	Crude MPR mean	Adjusted MPR mean* (95%CI)			
20-49y (n=24,957)											
No.=1-2 (n=6,827)	76.7	76.6 (75.6-77.6)	75.8	74.7 (73.4-76.0)	82.3	84.1 (80.2-88.0)	83.4	84.8 (83.4-86.1)	<0.01	0.7	0.78
No.=3-4 (n=11,768)	78.2	78.5 (77.6-79.3)	78.6	77.5 (76.8-78.3)	85.6	86.7 (85.2-88.2)	83.9	85.1 (84.1-86.1)	<0.01	-1.6	0.01
No.=5-6 (n=4,595)	78.1	78.6 (77.4-79.8)	76.7	75.3 (74.0-76.6)	82.2	83.9 (81.6-86.3)	84.2	85.3 (83.5-87.0)	<0.01	1.3	0.70
No.=7-9 (n=1,360)	79.4	79.3 (76.9-81.2)	77.5	76.7 (74.1-79.4)	76.7	78.6 (74.5-82.7)	81.9	82.4 (79.0-85.8)	<0.01	3.8	0.13
No.≥9 (n=407)	68.7	67.1 (62.6-71.6)	72.4	68.0 (63.1-73.0)	73.2	81.4 (74.0-88.8)	86.5	89.8 (82.4-97.1)	<0.01	8.4	0.05
50-64y (n=46,085)											
No.=1-2 (n=7,933)	81.8	81.9 (81.0-82.9)	81.4	81.0 (80.1-81.9)	88.9	89.2 (85.6-92.9)	88.5	89.3 (87.8-90.7)	<0.01	0.1	0.45
No.=3-4 (n=20,396)	82.5	83.0 (82.4-83.6)	83.2	82.3 (81.9-82.8)	88.3	89.5 (88.3-90.6)	89.1	90.4 (89.6-91.2)	<0.01	0.9	0.72
No.=5-6 (n=11,657)	83.5	83.7 (83.0-84.4)	83.8	83.2 (82.6-83.9)	87.8	88.5 (87.3-89.8)	90.3	91.1 (90.0-92.1)	<0.01	2.5	<0.01
No.=7-9 (n=4,438)	83.4	83.4 (82.2-84.5)	82.5	80.4 (79.2-81.5)	81.9	85.1 (83.1-87.1)	89.9	92.3 (90.6-94.0)	<0.01	7.2	<0.01
No.≥9 (n=1,661)	79.2	78.8 (76.9-80.6)	81.5	78.7 (76.7-80.8)	78.2	83.4 (80.3-86.4)	89.6	91.3 (88.3-94.3)	<0.01	7.9	<0.01
65-74y (n=30,652)											
No.=1-2 (n=3,412)	81.3	82.5 (80.6-84.4)	81.1	80.3 (79.2-81.4)	88.8	91.1 (85.5-96.8)	88.9	91.0 (88.3-93.8)	<0.01	-0.1	0.94
No.=3-4 (n=11,308)	83.5	83.9 (83.0-84.8)	83.0	82.5 (81.9-83.1)	88.7	89.2 (87.5-90.9)	90.3	91.6 (90.3-92.9)	<0.01	2.4	0.03
No.=5-6 (n=9,267)	83.1	83.1 (82.3-84.0)	82.7	82.3 (81.6-83.0)	88.0	88.3 (86.8-89.8)	91.5	92.5 (91.2-93.8)	<0.01	4.2	<0.01
No.=7-9 (n=4,562)	81.3	81.7 (80.5-82.9)	81.7	80.4 (79.3-81.5)	85.4	87.4 (85.4-89.4)	90.8	92.5 (90.7-94.4)	<0.01	5.2	<0.01
No.≥9 (n=2,103)	79.8	79.3 (77.5-81.1)	79.1	77.1 (75.4-81.1)	78.6	83.1 (79.9-86.2)	90.2	92.5 (89.5-95.6)	<0.01	9.5	<0.01
>=75y (n=14,983)											
No.=1-2 (n=1,351)	80.6	81.0 (77.1-84.9)	75.7	75.5 (73.8-77.3)	82.4	83.1 (72.1-94.0)	85.4	85.9 (80.3-91.5)	<0.01	2.9	0.69
No.=3-4 (n=4,916)	79.2	80.4 (78.7-82.1)	78.5	77.9 (77.0-78.9)	85.2	85.6 (82.6-88.6)	87.4	88.8 (86.3-91.2)	<0.01	3.2	0.42
No.=5-6 (n=4,586)	79.8	80.5 (79.0-82.0)	77.4	76.5 (75.4-77.6)	83.4	85.2 (82.6-87.8)	88.7	90.4 (87.9-92.8)	<0.01	5.2	0.01
No.=7-9 (n=2,711)	79.3	79.6 (77.9-81.4)	76.8	75.8 (74.3-77.2)	83.1	85.3 (82.3-88.2)	87.6	89.4 (86.4-92.3)	<0.01	4.1	0.18
No.≥9 (n=1,419)	77.8	77.4 (75.1-79.7)	75.5	74.9 (72.8-77.0)	80.2	81.3 (77.1-85.4)	85.7	88.6 (84.2-93.0)	<0.01	7.4	0.06

ARB,angiotensin II receptor blockers; CCB,calcium channel blockers; SPC,single pill combination; MPC,multiple pill combination; MPR, Medication possession ratio; CI, confidence interval

* Adjusted for factors associated with the patient (age, sex), condition (comorbidity), therapy (drug costs, number of concurrent drugs, prescription period), the healthcare system (insurance coverage), and the

social/economic status (income, residence)

† p value of crude MPR mean

‡ MPR differences = adjusted MPR of SPC group – adjusted MPR of MPC group

§ p value of MPR differences.

Analyses were performed using ANCOVA

Figure 1 Study population and data collection

ARB (angiotensin II receptor blockers), CCB (calcium channel blockers), MPC (multiple pill combination), SPC (single pill combination)

Figure 2 Trends of medication adherences according to age group and the number of medications

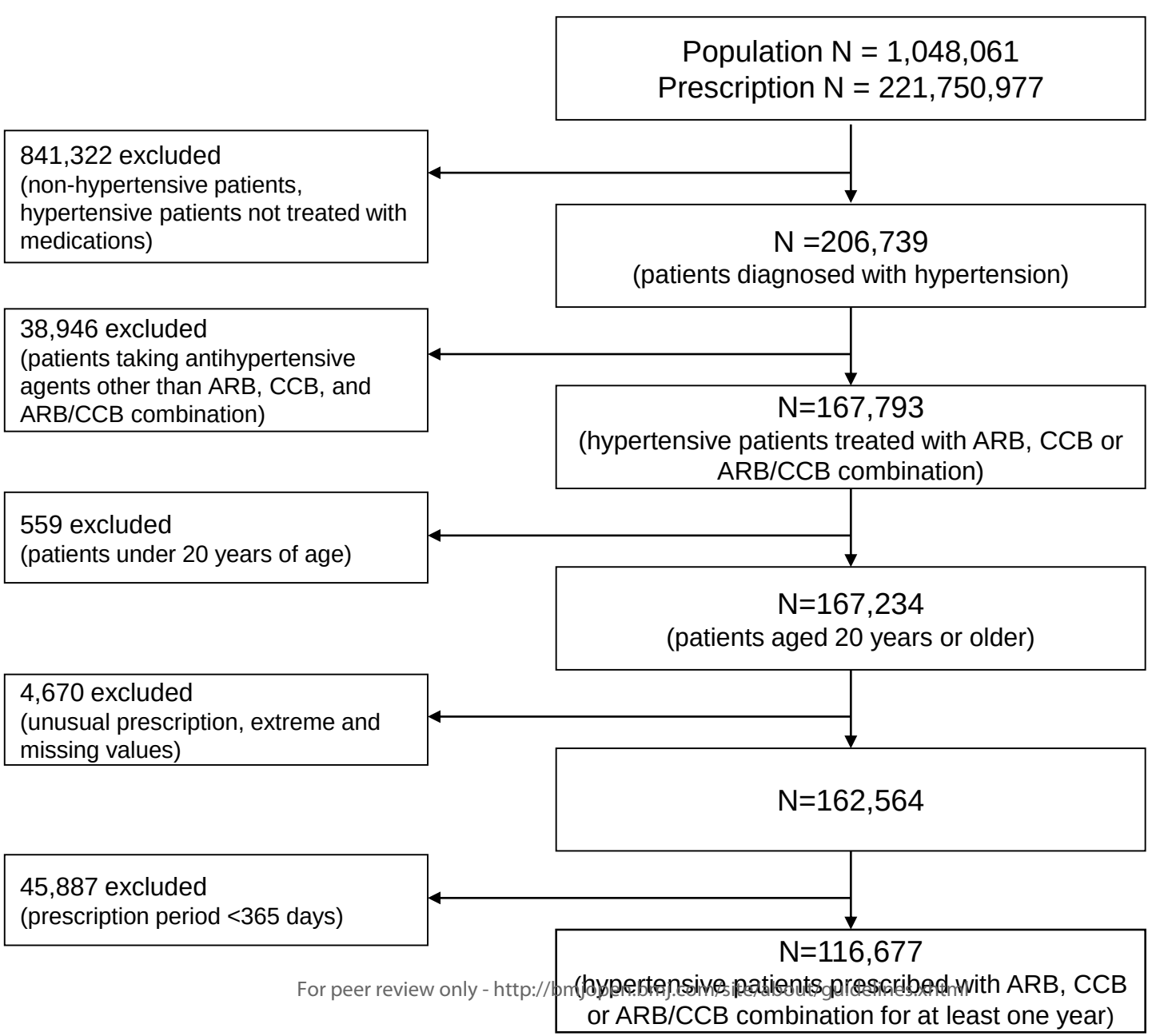
MPC (multiple pill combination), SPC (single pill combination), MPR (medication possession ratio), ARB (angiotensin II receptor blockers), CCB (calcium channel blockers)

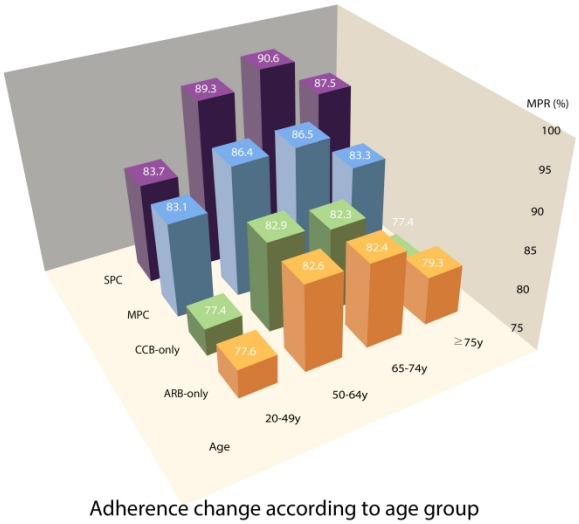
Figure 3 Difference of medication adherences between MPC and SPC therapies according to combinations of pill numbers and age

The number of drugs for which the adherence difference begins to increase is 3-4 in the elderly group (≥65year) and 5–6 in the non-elderly group (20–64year) ($p<0.05$).

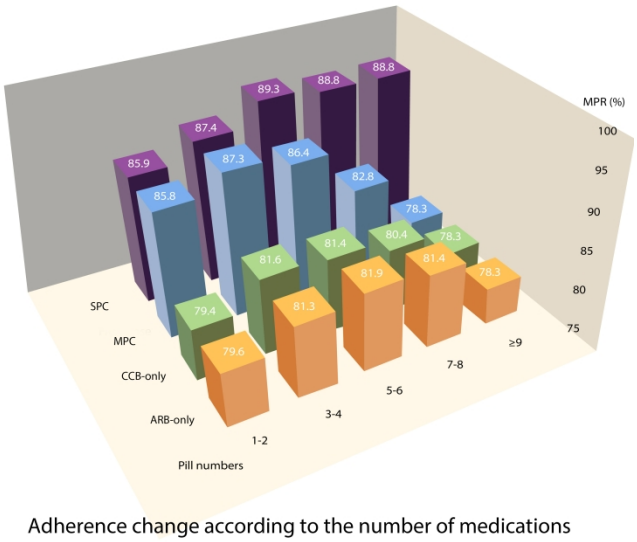
MPC (multiple pill combination), SPC (single pill combination), MPR (medication possession ratio)

*MPR difference = MPR of SPC group – MPR of MPC group





Adherence change according to age group



Adherence change according to the number of medications

Figure 2 Trends of medication adherences according to age group and the number of medications
MPC (multiple pill combination), SPC (single pill combination), MPR (medication possession ratio), ARB (angiotensin II receptor blockers), CCB (calcium channel blockers)

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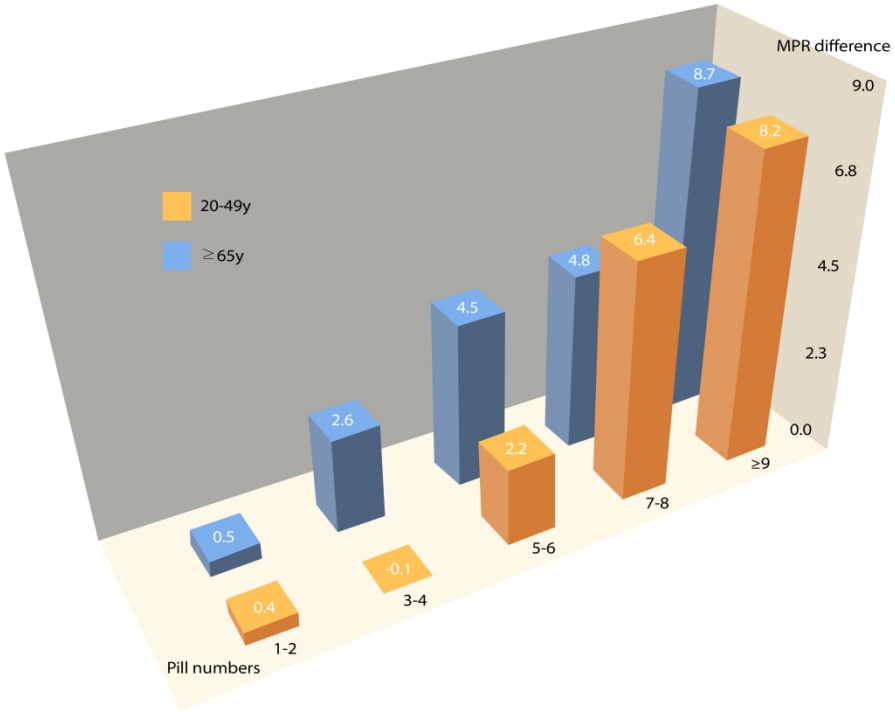
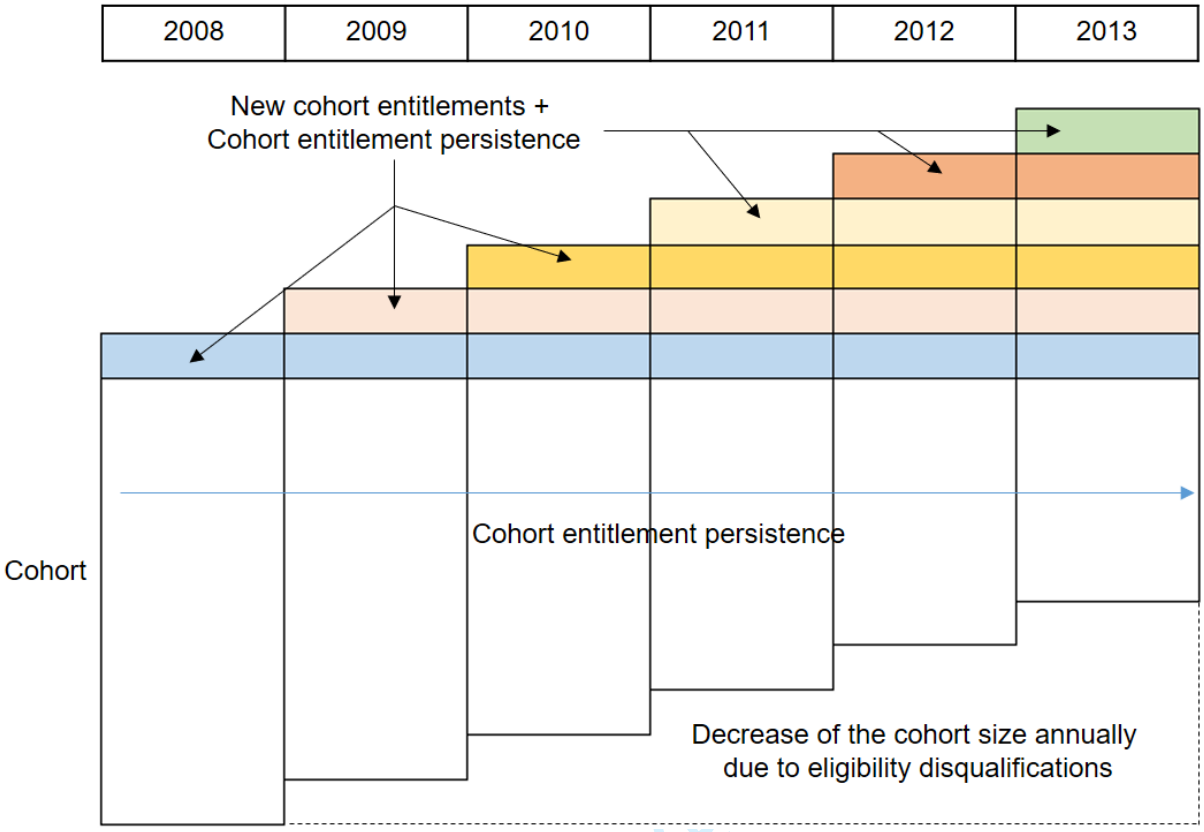


Figure 3 Difference of medication adherences between MPC and SPC therapies according to combinations of pill numbers and age

The number of drugs for which the adherence difference begins to increase is 3-4 in the elderly group (≥65year) and 5–6 in the non-elderly group (20–64year) ($p<0.05$). MPC (multiple pill combination), SPC (single pill combination), MPR (medication possession ratio) *MPR difference = MPR of SPC group – MPR of MPC group

338x277mm (300 x 300 DPI)

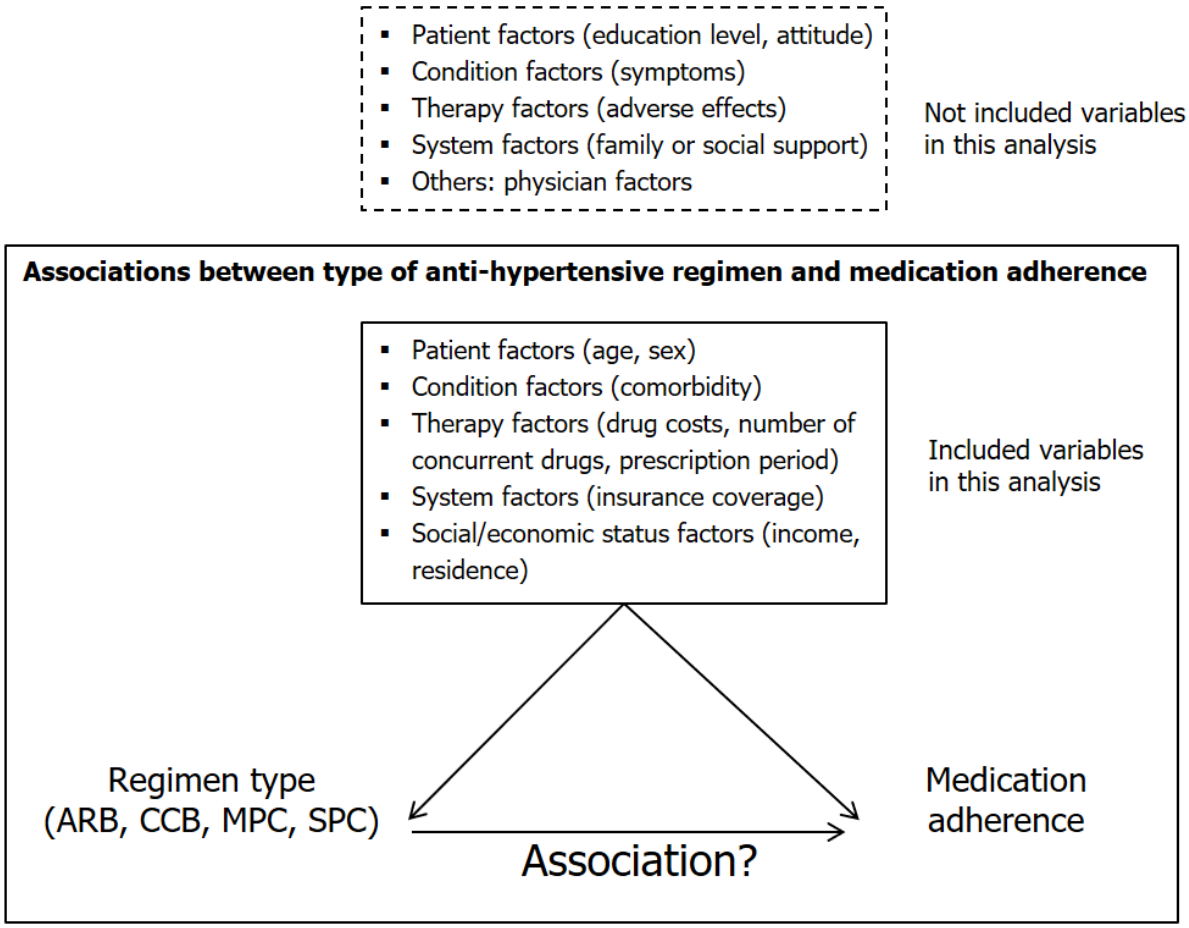
Supplementary online contents. A single pill combination of antihypertensives does improve adherence: A Korean nationwide study



Supplementary figure 1 Dynamic cohort design

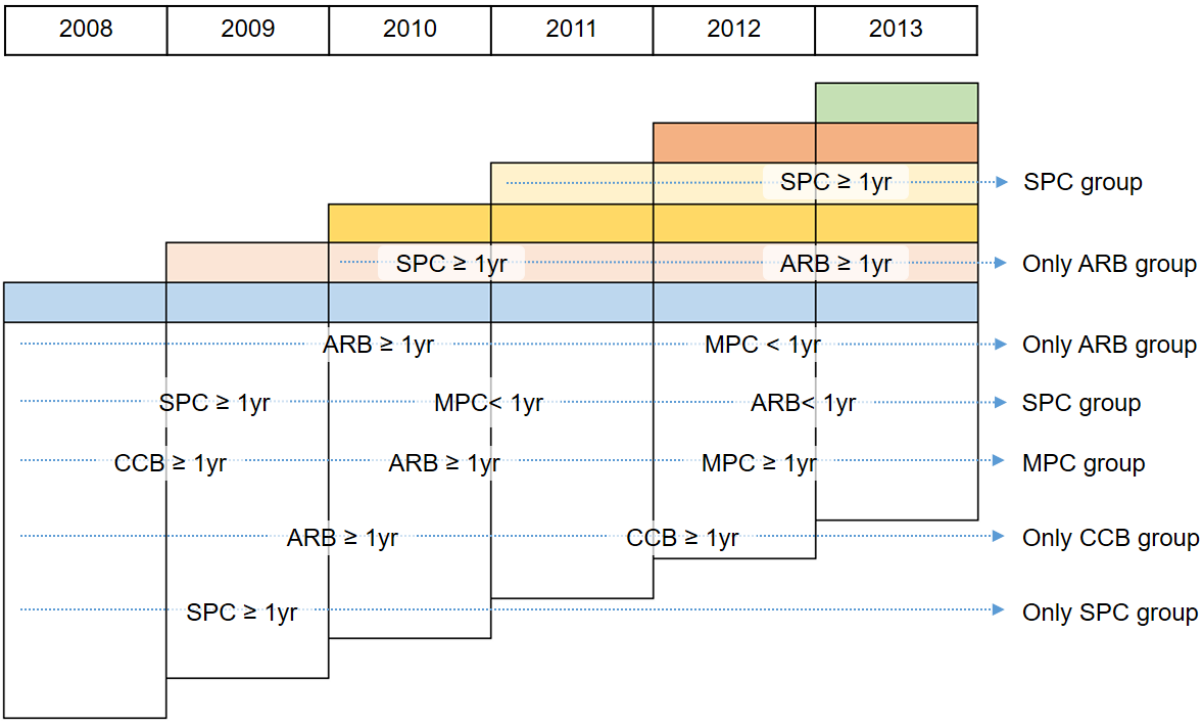
Cohort size: About one million/year (2.2% of total population)

Cohort data include qualification data (birth, death, sex, family relationship, address, property, income, insurance type) and medical service use data (billing statement, medical records, diagnosis record, prescription record, etc.)



Supplementary figure 2 Analysis scheme for factors related with anti-hypertensive medication adherence

ARB (angiotensin II receptor blockers), CCB (calcium channel blockers), MPC (multiple pill combination), SPC (single pill combination)



Supplementary figure 3 Classification definition of anti-hypertension medication groups

ARB (angiotensin II receptor blockers), CCB (calcium channel blockers), SPC (single pill combination), MPC (multiple pill combination)

STROBE Statement—checklist of items that should be included in reports of observational studies

Title and abstract	1.	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was found. **(mentioned in page 1-4 of the manuscript)**
Introduction		
Background/rationale	2.	Explain the scientific background and rationale for the investigation being reported. **(mentioned in page 5 of the manuscript)**
Objectives	3.	State specific objectives, including any prespecified hypotheses. **(mentioned in page 5-6 of the manuscript)**
Methods		
Study design	4.	Present key elements of study design early in the paper. **(mentioned in page 7-8 of the manuscript)**
Setting	5.	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow up, and data collection. **(mentioned in page 7-11 of the manuscript)**
Participants	6.	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(mentioned in page 7-11 of the manuscript)**
Variables	7.	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. **(mentioned in page 8-10 of the manuscript)**
Data source/measurement	8.	For each variable of interest, give sources of data and details of method of assessment (measurement). Describe comparability of assessment methods if there is more than one group. **(mentioned in page 7-11 of the manuscript)**
Bias	9.	Describe any efforts to address potential sources of bias. **(mentioned in page 7-11 of the manuscript)**
Study size	10.	Explain how the study size was arrived at.

		(mentioned in page 7-8 of the manuscript)
Quantitative variables	11.	Explain how quantitative variables were handled in the analyses. **(mentioned in page 7-9 of the manuscript)**
Statistical methods	12.	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) If applicable, explain how loss to follow-up was addressed. **(mentioned in page 9-11 of the manuscript)**
Results		
Participants	13.	(a) Report numbers of individuals at each stage study- eg, numbers of potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow up. And analysed. (b) Give reasons for non-participation at each age. (c) Consider use of a flow diagram. **(mentioned in page 12-13 of the manuscript)**
Descriptive data	14.	(a) Give characteristics of study participants (eg, demographic, clinical social) and information on exposures and potential confounders. (b) Indicate number of participants with missing data for each variable of interest. **(mentioned in page 12 of the manuscript)**
Outcome data	15.	Report numbers of outcome events or summary measures over time. **(mentioned in page 12-13 of the manuscript)**
Main results	16.	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimated and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **(mentioned in page 12-13 of the manuscript)**
Other analyses	17.	Report other analyses done- eg, analyses of subgroup and interactions, and sensitivity analyses.

		(mentioned in page 13 of the manuscript)
Discussion		
Key results	18.	Summarise key results with reference to study objectives **(mentioned in page 14-19 of the manuscript)**
Limitations	19.	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(mentioned in page 19 of the manuscript)**
Interpretation	20.	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. **(mentioned in page 14-19 of the manuscript)**
Generalisability	21.	Discuss the generalisability (external validity) of the study results. **(mentioned in page 14-19 of the manuscript)**
Other infromation		
Funding	22.	Give the source of funding and the role of the finders for the present study and, if applicable, for the original study on which the present article is based. **(mentioned in page 20 of the manuscript)**