Original Article

Medication Adherence Improvement By Using Administration Timing Simplification Protocol (ATSP) in Cardiovascular Disease Patients

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Aims: In chronic diseases, keeping adherence to medication is very difficult. The objective of this study was to evaluate the impact of administration timing simplification protocol (ATSP) on medication adherence and clinical parameters of cardiovascular diseases.

Methods: 210 out-patients with cardiovascular disease, who were taking two or more pills of any type of medication per day for more than one year, were enrolled and randomized. The intervention group followed the simplified administration schedule of ATSP with two main strategies: 1) moving medication from "pc" (30 minute after meal) to "stat. pc" (immediately after meal); and 2) moving medication time from "at evening" to "at morning." In contrast, the control group maintained the same medication schedule. Both patient groups were equally educated about the names and effects of the medication.

Results: The intervention group had more pills than the control group with marginal statistical significance (5.1 ± 2.3 vs 4.6 ± 1.8, $p = 0.05$). The total frequency of administration was significantly higher in the intervention group than that of the control group (2.9 ± 1.0 vs 2.6 ± 0.9, $p = 0.03$) at the baseline. In the intervention group, the frequency was significantly decreased to 1.5 ± 0.6 times per day after following ATSP application ($p < 0.01$). In both patient groups, knowledge about the medication was significantly improved by education. However, medication adherence was only improved in the intervention group. Interestingly, total cholesterol was significantly decreased in the intervention group ($p < 0.01$). The decrease in serum cholesterol concentration was significantly correlated with the improvement in medication adherence evaluated with Morisky Medication Adherence Scale (MMAS)-8 items ($r = 0.507$, $p < 0.01$).

Conclusion: ATSP was shown to be an effective strategy to improve medication adherence in chronic cardiovascular disease patients.

Key words: Medication adherence, Compliance, Cardiovascular patients

Introduction

Medication adherence refers to the degree or the extent of conformity to recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency[1]. Medication adherence is often suggested to have bigger impact than medication choice on patient outcome[2]. However, most cardiovascular diseases such as hypertension, hypercholesterolemia, and diabetes mellitus are chronic diseases. Keeping medication adherence for these chronic diseases is very difficult[3-5]. For example, in Korea, the rate of non-adherence to antihypertensive medication has reached 41%[6, 7]. It has been suggested that twice

as many cardiovascular deaths might have been prevented by improving adherence rate from 50% to 75%[8]. Patient factors, drug factors, and other factors such as the patient-provider relationship, cost of medication, and regimen complexity are barriers to medication adherence[9, 10]. Therefore, tailored managements are essential to overcome these barriers[11].

Previous studies have reported heterogeneous association between medication adherence and administration complexity. In general, it is believed that increased numbers or frequent administration times of medications are associated with lower medication adherence[12]. However, a recent Cochrane systematic review has shown that most intervention trials failed to improve clinical outcomes[13]. Besides complexity of medication administration, education about medication has also been suggested as one possible factor that influences medication adherence[14]. Although many studies have tried various interventions to improve drug adherence[14-17], there have been no strict intervention by simplifying medication timing without changing prescription.

The objective of this study was to evaluate the impact of the administration timing simplification protocol (ATSP) on medication adherence rate and the clinical parameters of cardiovascular diseases. We also hypothesized that pharmacist's counseling had a significant impact on patients' knowledge about their medication and medication adherence.

Methods

Study Design

This is a randomized controlled trial investigating the effectiveness of an ATSP intervention on medication adherence and clinical measures compared with usual care at 3 months. 210 out-patients ≥18 years old with cardiovascular diseases such as hypertension, hyperlipidemia, diabetes mellitus, and other comorbidities including angina, myocardial infarction, and heart failure, who were taking two or more pills of any type of medication per day for more than one year, were enrolled. Patients were excluded if they had diagnosis of communication disorders, cognitive impairment, or dementia. All patients provided written informed consent before enrollment. The study protocol followed the SPIRIT guidelines and conformed to the Declaration of Helsinki. It was approved by the Institutional Review Board of Seoul National University Hospital (H-1401-123-549). And it was registered in Clinical Research Information Service (CRiS) of the Republic of Korea (KCT0002023). Patients were randomly assigned either to the control group or to the intervention group by even allocation according to which day

of the week their clinical appointment took place. Therefore, in one day (for example, Monday) all enrolled patients were allocated in the same group. However, the randomization was concealed from the clinicians who enrolled/treated the patients. The clinicians only recruited the patients and introduced them to the research pharmacist, who assigned the group of the day. Also, the group of the day was randomly changed. Both groups were equally educated by one research pharmacist about the name and effect of their prescribed medication. Patients were requested to bring their remaining pills to the clinic in every visit including the baseline and follow up visit. To minimize potential selection bias, patients' medical records were collected after allocation.

Administration Timing Simplification Protocol (ATSP)

For intervention group, ATSP was applied at the baseline. ATSP has the following two main strategies: 1) move medication from "pc" (30 minute after meal) to "stat. pc" (immediately after meal); and 2) move from "at evening" to "at morning." This change in administration timing was based on previous research findings for cardiovascular disease medication. The main strategies of ATSP are summarized in **Supplemental Table 1**[18, 19, 37, 38]. In contrast, the control group was maintained on the usual administration timing as licensed by Korea Ministry of Food and Drug Safety throughout the study.

Data Collection

The research pharmacist interviewed patients to collect the baseline data including numbers and administration timing of medication with a self-reported questionnaire for brief medication knowledge. Clinical parameters such as blood pressure, glycated hemoglobin, and lipid profile were measured at the baseline and at 3-month follow-ups. For medication adherence, self-reported medication adherence and actual remain pill counts were also surveyed at the baseline and at the 3-month follow-ups.

Self-reported questionnaire for brief medication knowledge (SQBMK) is a revised simple and self-reported form of brief medication questionnaire (BMQ). It was designed for patients with chronic diseases[20]. SQBMK focused on medication knowledge such as the name and effect of drug, and the patients were classified into no knowledge, some knowledge, or good knowledge groups based on their responses (**Supplemental Table 2**).

Self-reported Morisky Medication Adherence Survey (MMAS)-8 items scale for medication adherence[21] and self-reported Yes/No response items were
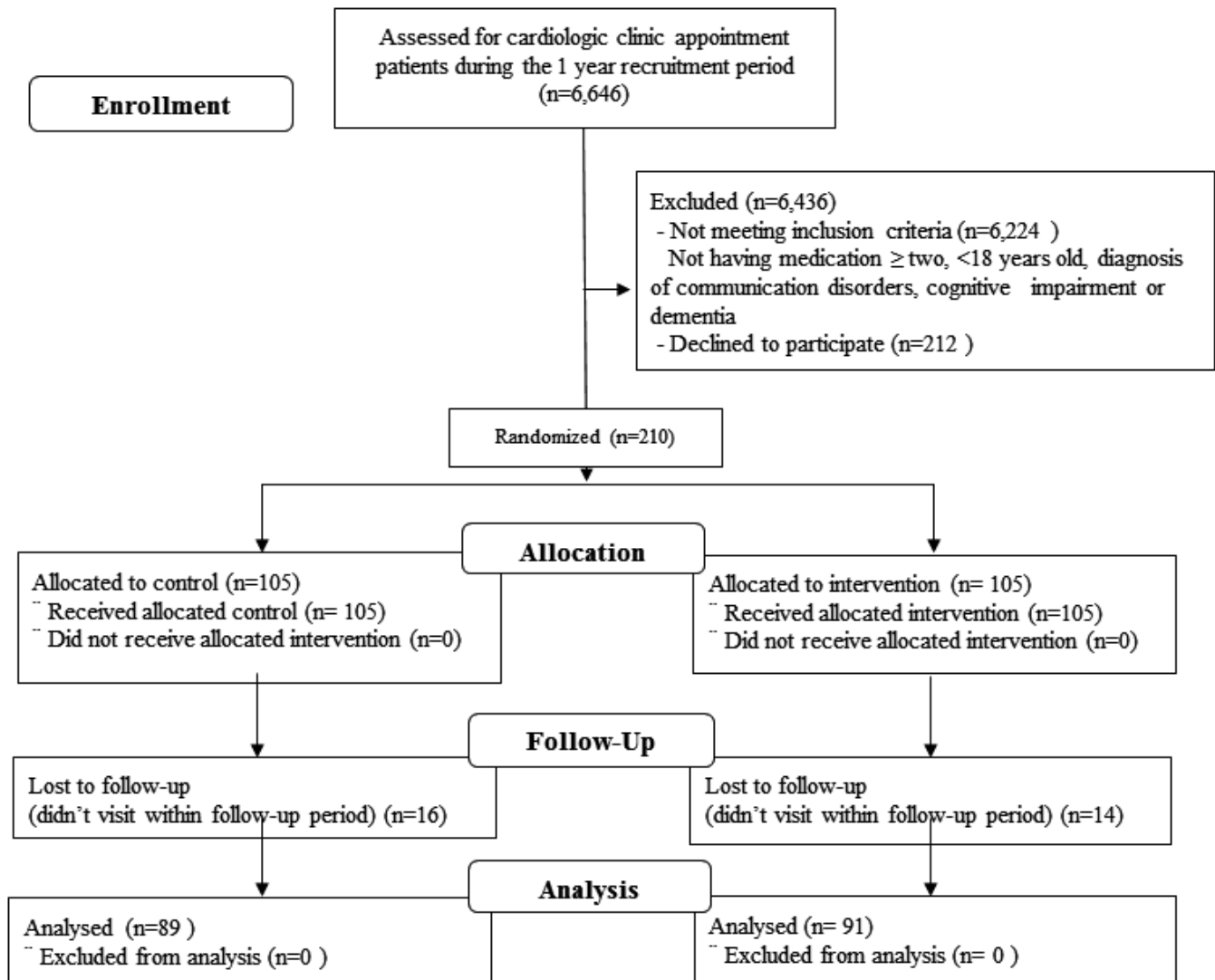
Fig. 1. Study flow chart.

used to determine medication adherence considering the ways that medication omission could occur. Briefly, response choices were Yes or No for items 1–7. A 5-point Likert response scale was used for the last item (item 8). A Korean translation of the MMAS-8 items was used and adapted specifically for cardiovascular disease medication in this study[22]. Direct pill counts were also used to evaluate medication adherence when patients returned to the clinic for their refill prescription. At the baseline, the patients were prescribed the exact amount of medication for the next visit, which was used as denominator for the adherence calculation[23]. Pill count percentage (%) was calculated by (total pills – remained pills) divided by total prescription pills.

Statistical Analysis

To calculate the target sample size for this trial, effect size as medium 0.5 between the two groups independent Student's t-test in accordance with results of previous meta-analyses for the estimation of medication adherence was used[17, 19]. With a statistical power of 95% and a type 1 error of 5%, 2-sided, the target sample size was estimated to be 210 subjects (105 per group) using G-power program (version 3.1.7, Franz Faul, University Kiel, Germany). 210 patients who completed follow up assessment were analyzed. Data were analyzed mainly in the intention-to-treat (ITT) group and also in the per-protocol (PP) group.

Data were presented as mean ± standard deviation for normally distributed data and as median with interquartile ranges for data without normal distribu-

Table 1. Baseline characteristics of patients

	Control group (N = 105) Mean ± SD	Intervention group (N = 105) Mean ± SD	Total (N = 210) Mean ± SD
Demographics			
Age (year)	66.2 ± 10.4	66.5 ± 9.2	66.3 ± 9.8
Male of participants (%)	53.3	59.0	56.2
Duration of cardiovascular disease (year)	3.7 ± 2.8	3.7 ± 2.9	3.7 ± 2.8
Duration of follow up (day)	101.4 ± 31.7	107.1 ± 33.1	104.2 ± 32.4
Disease prevalence (%)			
Hypertension	97.1	96.2	96.7
Diabetes Mellitus	40.0	53.3	46.7
Hyperlipidemia	94.3	97.1	95.7
Others	71.4	69.5	70.5
Medication (n)			
Total tablets taken in a day	4.6 ± 1.8	5.1 ± 2.3	4.9 ± 2.1
Anti-hypertensive agents	1.7 ± 0.8	1.8 ± 1.0	1.8 ± 0.9
Oral hypoglycemic agents	0.7 ± 1.0	1.0 ± 1.2	0.9 ± 1.1
Anti-hyperlipidemic agents	1.0 ± 0.4	1.0 ± 0.3	1.0 ± 0.4
Anti-platelet agents	0.9 ± 0.7	1.0 ± 0.9	0.9 ± 0.8
Others	0.4 ± 0.9	0.3 ± 0.9	0.4 ± 0.9

*Analysis conducted by independent student t-test and Chi-square test. There were no statistically significant differences between the control group and the intervention group except slightly larger total tablet number in the intervention group with marginal significance than control group ($p = 0.05$).

tion. For comparison between two groups, Chi-square of Fisher's exact test was used for categorical variables, while unpaired Student's t-test was used for continuous variables. One-way analysis of variance (ANOVA) was used to determine differences for continuous variables among more than two groups. Two-sided p values less than 0.05 were considered as statistically significant in all analyses. All statistical tests were performed using SPSS statistics for medical service (version 22.0, IBM Corp. USA).

Results

Baseline Characteristics of the Study Population

Of 6,646 screened subjects of out-patient clinic patients list, 210 patients were enrolled and randomly assigned to the intervention group ($n = 105$) and the control group ($n = 105$). Among them, 14 (13%) patients in the intervention group and 16 (15%) patients in the control group discontinued the study (**Fig. 1**). The subject demographics and baseline characteristics are presented in **Table 1**. No demographic parameters appeared to differ significantly between two groups except slightly larger total tablet number in the intervention group with marginal significance than control group (5.1 ± 2.3 vs 4.6 ± 1.8, $p = 0.05$). Most taken medications were antihypertensive drugs

(1.8 ± 0.9 pills/day, range: $0 - 6$), anti-hyperlipidemic agents (1.0 ± 0.4 pills/day, range: $0 - 2$), and oral hypoglycemic drugs (0.9 ± 1.1 pills/day, range: $0 - 5$). Other medications included aspirin, clopidogrel, allopurinol, famotidine, digoxin, folic acid, thioctic acid, vitamin B complex, and ferrous sulfate.

Medication Schedule Adjustment According to ATSP

The total frequency of administration was significantly greater in the intervention group than that in the control group at the baseline (2.9 ± 1.0 vs 2.6 ± 0.9, $p = 0.03$). In the control group, the frequency of medication administration was not changed between the baseline and the follow-up. On the other hand, in the intervention group, medication frequency was significantly reduced from 2.9 ± 1.0 times per day to 1.5 ± 0.6 times per day after following ATSP application ($p < 0.01$). At 3-months follow-up, the total frequency of administration was significantly lower in the intervention group (1.5 ± 0.6 times per day) compared to the control group (2.6 ± 0.9 times per day), as shown in **Fig. 2** ($p < 0.01$).

The total number of medication administration time schedules that were modified by ATSP was 310 times. Strategy 1 ATSP of moving administration timing from "30 minute after meal (pc)" to "immediately
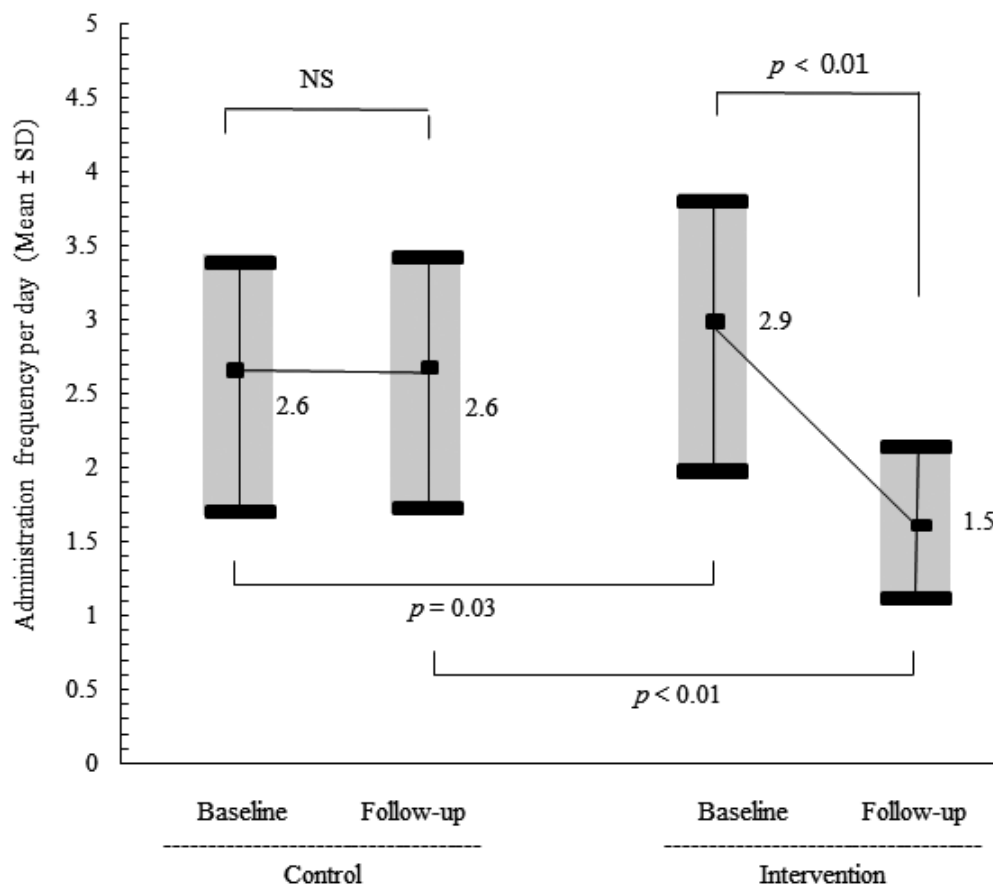
Fig. 2. Administration frequency in the control group and the intervention group. NS=No statistical significance

after meal (stat. pc)" was applied in 259 time schedules. Strategy 2 ATSP of switching administration timing from "evening intake" to "morning intake" was applied in 51 time schedules. Number of ATSP application and specific strategy applied for individual medication classes are presented in **Supplemental Table 3**.

Changes of Medication Knowledge and Adherence

Medication knowledge was evaluated using self-reported questionnaires for brief medication knowledge (SQBMK) at the baseline and follow up. More than 40% were classified as having no knowledge and less than 15% had good knowledge at the baseline. In both groups, medication knowledge was significantly improved by education. There was no significant difference in medication knowledge either at the baseline ($p=0.82$) or at follow up ($p=0.72$) between the two groups (**Supplemental Fig. 1** and **Supplemental Table 4**).

There was no statistically significant difference in medication adherence measured by Morisky Medica-

tion Adherence Survey (MMAS)-8 at the baseline (intervention group 48.6% vs. control group 45.7%, $p=0.70$). At 3-months follow-up, the intervention group had a significantly higher proportion of high-adherent patients compared to control group (intervention group 80.2% vs. control group 56.2%, $p<0.01$) (**Fig. 3A**, **Supplemental Table 5**). However, the control group showed no significant change in the proportion of patients with high adherence between the baseline and follow up ($p=0.11$). Average scores of the MMAS-8 item changes were also significantly higher in the intervention group compared to that in the control group (**Supplemental Table 6**). There was no statistically significant difference in the proportion of patients with high adherence measured by pill count at the baseline (intervention group 72.4% vs. control group 81.0%, $p=0.35$); however at 3-months follow-up, the intervention group had a significantly higher proportion of high-adherent patients compared to control group (intervention group 90.1% vs. control group 70.8%, $p=0.01$) (**Fig. 3B**).
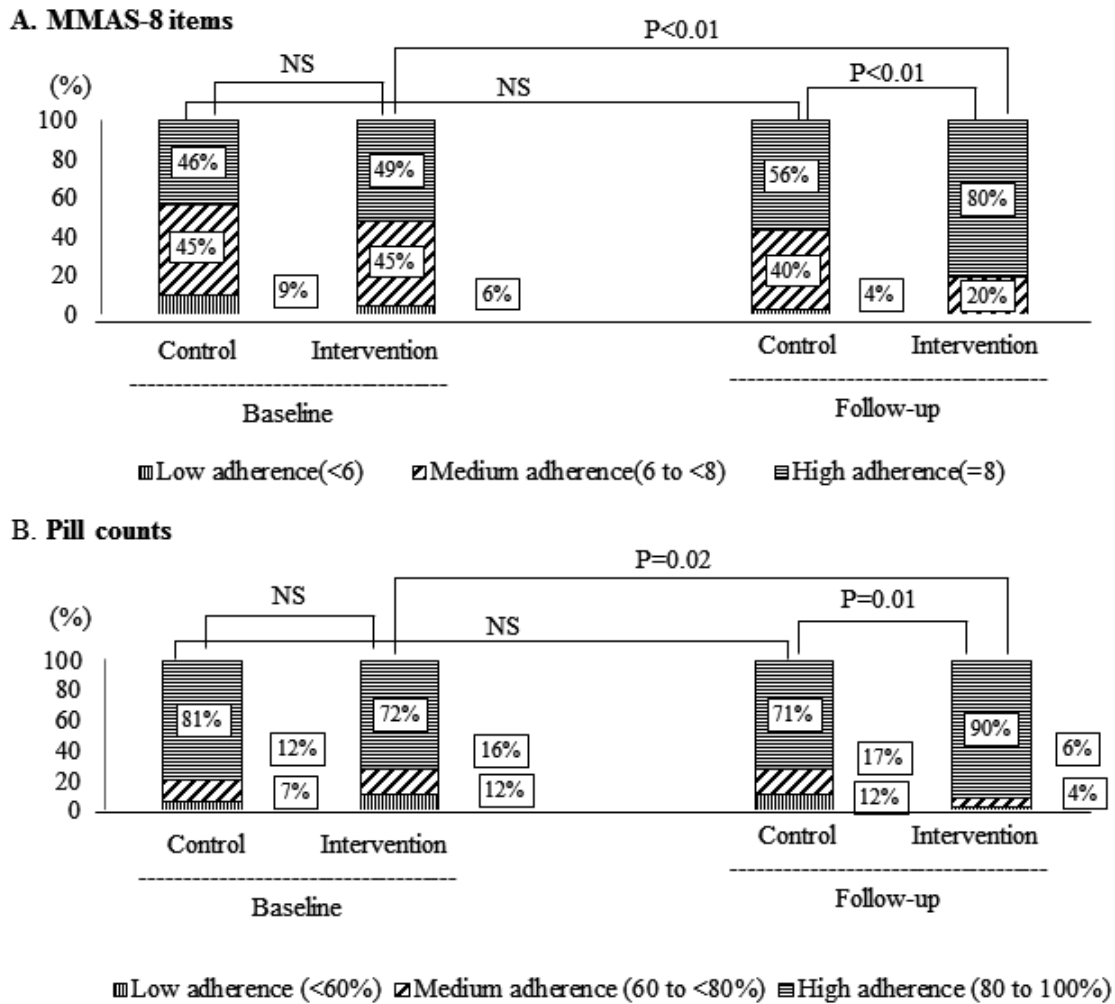
A. MMAS-8 items

B. Pill counts

Fig. 3. Medication adherence at baseline and follow up assessment point. NS = No statistical significance

Changes in Clinical Parameters

Blood pressures and glycated hemoglobin (HbA1c) were not significantly changed from the baseline to follow up in either group. Total cholesterol levels were significantly decreased in the intervention group from the baseline to follow up compared control group (160.4 ± 30.7 mg/dl to 148.3 ± 24.8 mg/dl, $p < 0.01$). However, there were no significant changes in total cholesterol levels in the control group between the baseline and follow up. As a result, total cholesterol levels were significantly different in the intervention group and control group (159.4 ± 34.2 mg/dl to 148.3 ± 24.8 mg/dl, $p = 0.02$) (**Table 2**).

Correlation analysis results revealed that the decrease in serum cholesterol concentration was significantly correlated ($r = 0.507$, $p < 0.01$) with improvement in medication adherence based on self-reported MMAS-8 items.

Discussion

This study showed that simplifying administration schedule was a very effective strategy in improving medication adherence. The first strategy was by merging medication timing of 30 minute after meal (*pc*) to immediately after meal (*stat. pc*). The second strategy was by moving administration timing from evening to morning. Simplifying the administration schedule was possible because most antihypertensive agents such as amlodipine are not greatly affected by food and meals. On the other hand, for example, metformin, an oral hypoglycemic agent, is recommended to be taken immediately after a meal to alleviate abdominal discomfort. Therefore, we arranged the administration schedule of antihypertensive medication to immediately after meal together with the administration with metformin. Recent anti-hyperlipidemic agents, such as rosuvastatin and atorvastatin,

Table 2. Changes in key clinical parameters

	Baseline			Follow-up		
	Control group N=105 Mean ± SD	Intervention group N=105 Mean ± SD	*p*-value	Control group N=89 Mean ± SD	Intervention group N=91 Mean ± SD	*p*-value*
Systolic BP (mmHg)	127.4 ± 12.7	127.2 ± 12.8	0.47	128.7 ± 13.0	126.8 ± 10.3	0.69
Diastolic BP (mmHg)	76.5 ± 9.0	75.7 ± 8.7	0.49	76.7 ± 9.1	76.1 ± 8.6	0.61
HbA1c (%)	6.4 ± 1.3	6.8 ± 0.7	0.15	6.8 ± 0.8	6.7 ± 0.6	0.67
Low density lipoprotein (mg/dl)	83.1 ± 27.4	81.5 ± 25.2	0.65	82.4 ± 29.3	78.6 ± 21.1	0.45
High density lipoprotein (mg/dl)	51.6 ± 12.3	50.2 ± 15.2	0.50	50.2 ± 13.8	48.1 ± 13.6	0.44
Total cholesterol (mg/dl)	157.2 ± 30.2	160.4 ± 30.7	0.45	159.4 ± 34.2	148.3 ± 24.8	0.02
Triglyceride (mg/dl)	142.5 ± 77.6	144.8 ± 68.6	0.72	143.0 ± 102.5	135.9 ± 61.4	0.28

*Analysis conducted by independent student *t*-test. *P*-value < 0.05 was statistically significance

have similar results being administered either in the morning or in the evening due to their long half-time over 12 hours. Therefore, statins could be moved from "the default" evening administration to morning administration with other morning pills. In addition, key clinical parameters, including serum cholesterol levels and blood glucose levels, were improved by simplifying administration timing.

Administration Timing Simplification for Improving Medication Adherence

The World Health Organization has recognized the importance of medication adherence for controlling chronic diseases[24]. Notwithstanding the importance of medication adherence, approximately 50% patients with cardiovascular diseases have poor adherence to their prescribed medications[25]. Moreover, non-adherence in the elderly resulted in over 30% loss in total medication doses due to forgetfulness and misunderstanding dose/method of administration[26]. It is often suggested that non-adherence to cardioprotective medications is associated with 10% to 40% relative increase in risk of cardiovascular hospitalizations and 50% to 80% relative increase in risk of mortality[27]. In order to overcome the non-adherence problem, simpler dosage regimens for all medications or devices that are easier to remember have been tried[28]. The most effective strategy to simplify a regimen might be by prescribing a pill that can be taken once a day[29]. In addition, scheduling intake of different drugs at the same time is also an effective strategy[26]. In this study, ATSP was found to be able to reduce medication frequency by changing administration times without decreasing the efficacy of each medication. As expected, this study showed that ATSP was very effective in improving medication adherence.

Increasing Medication Knowledge to Improve Medication Adherence

The barrier in patients' communication with healthcare givers might be another reason affecting adherence[30]. It has been reported that increasing the patient−clinician communication does not result in increased medication adherence[26]. Although most adherence interventions are typically focused on providing education to increase knowledge, available evidence has shown that this alone is not enough. A meta-analysis about adherence-enhancing interventions has concluded that combined interventions are more effective than single-focus education[31]. For heart failure, a randomized clinical study has demonstrated that intensive pharmacist-led intervention lead to a 10.9% improvement in adherence to cardiovascular medications compared to usual care[32]. In this study, the patients' knowledge about medication was significantly increased after pharmacist briefly educated them about the name and effect of their medications.

Influence of Medication Adherence on Clinical Outcomes

Poor adherence to cardiovascular medications is associated with increased number of cardiovascular-related emergency department visits[33]. Conversely, higher adherence (defined as medication possession ratio of 80% to 100%) to antihypertensive medications is associated with better control of blood pressure levels compared to that with medium or low levels of adherence[34]. However, the relationship between adherence and clinical outcomes is not always consistent. An important finding of this study was that we found it was possible to improve control of patients' key surrogate markers for cardiovascular risk by increasing medication adherence. Older statins such as

pravastatin and simvastatin had shorter durations of action. Even though simvastatin has a slightly better lipid-lowering effect when taken in the evening instead of in the morning, other factors such as compliance and non-lipid effects of statins may weaken the recommendation to give statins as evening medication[35]. Recent meta-analysis suggested that the main reasons for statin non-adherence included forgetfulness[36]. In this aspect, simplifying administration timing might be a very effective strategy to improve statin adherence. Moreover, considering their longer durations of action, current statins, such as atorvastatin and rosuvastatin, should be better prescribed in the morning with other medications to improve medication adherence.

In conclusion, this study showed that ATSP can be used as an effective strategy to improve medication adherence rate in chronic cardiovascular disease patients. Moreover, key clinical parameters including cholesterol and glucose levels were found to be improved after applying ATSP. There are some limitations such as short follow up period and relatively small population. Nevertheless, this study proposed the simplest way to improve the medication adherence.

Disclosures

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conception and design: Jung SH, Lee HY, Kim HS, Kwon KH. Acquisition of data: Jung SH, Lee OS. Analysis and interpretation of data: Jung SH, Lee HY. Critical comments for important intellectual content: Kim HS, Kwon KH. Writing or revision of the manuscript: Jung SH, Lee HY, Kwon KH. Study supervision: Lee HY, Kwon KH.

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Supplemental Table 1. Administration Timing Simplification Protocol (ATSP)

ATSP strategy	*Baseline*	Changed	Example Medication	Background references
1	*pc* (*30 minute after meal*)	*stat. pc* (immediately after meal)	amlodipine, atorvastatin, rosuvastatin, pitavastatin, fluvastatin XL, sitagliptin	18, 19, 37, 38
2	*at evening*	at morning	Atorvastatin, rosuvastatin, pitavastatin, fluvastatin XL	

Supplemental Table 2. Self-reported questionnaire for brief medication knowledge (SQBMK)

	Brand name of medication	Effectiveness of medication	Result
No knowledge	No	No	None of yes
Some knowledge	Yes or no	Yes or no	One of yes
Good knowledge	Yes	Yes	Both of yes

Supplemental Table 3. Change rate in administration timing for medication classes of cardiovascular diseases

ATSP	Control group	Intervention group					
		Medication class					
		Anti-hypertensive agent	Anti-hyperlipidemic agent	Oral hypoglycemic agent	Anti-platelete agent	Others	*p*-value[*]
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Application							
strategy 1	0 (0.0)	110 (58.5)	51 (48.1)	4 (3.7)	69 (65.7)	25 (71.4)	<0.01
strategy 2	0 (0.0)	0 (0.0)	51 (48.1)	0 (0.0)	0 (0.0)	0 (0.0)	
No application	507 (100.0)	78 (41.5)	4 (3.8)	103 (96.3)	36 (34.3)	10 (28.6)	

ATSP, Administration Timing Simplification Protocol
[*]Analysis conducted by ANOVA-test. *P*-value less than 0.05 was considered as statistically significant.
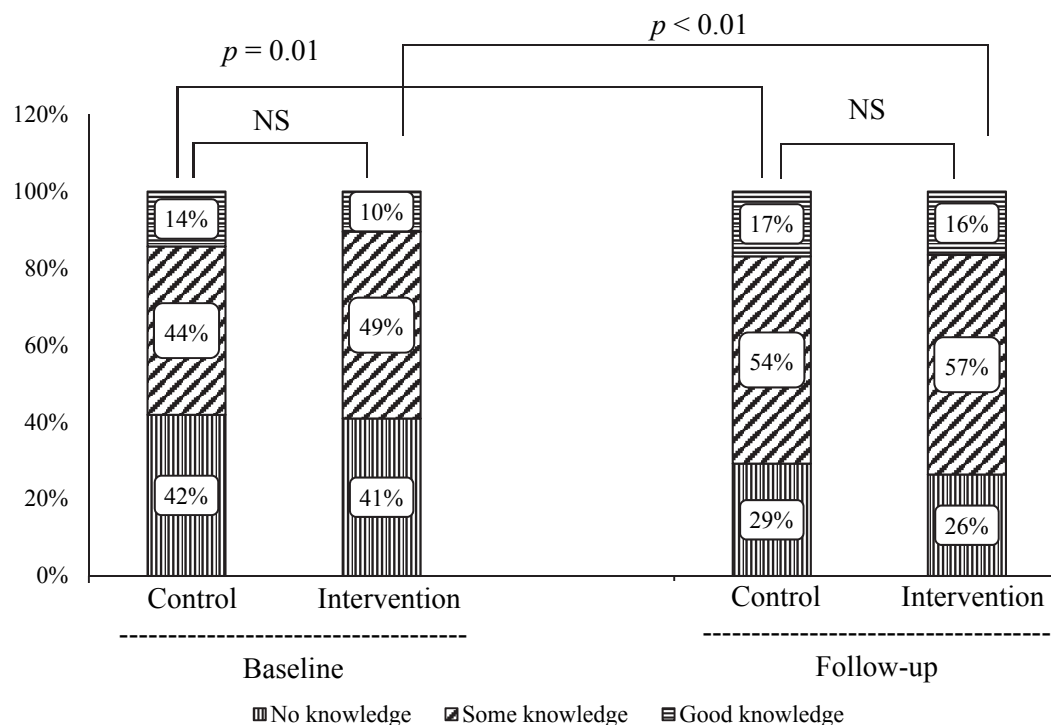
Supplemental Fig. 1. Self-reported questionnaire for brief medication knowledge (SQBMK) after pharmacist education.

Supplemental Table 4. Self-reported questionnaire for brief medication knowledge (SQBMK) after pharmacist education

	Baseline			Follow-up		
	Control group N=105 n (%)	Intervention group N=105 n (%)	p-value	Control group N=89 n (%)	Intervention group N=91 n (%)	p-value*
SQBMK			0.82			0.72
No knowledge	44 (41.9)	43 (41.0)		27 (30.3)	24 (26.4)	
Some knowledge	46 (43.8)	51 (48.6)		47 (52.8)	52 (57.1)	
Good knowledge	15 (14.3)	11 (10.5)		15 (16.9)	15 (16.5)	

*Analysis conducted by ANOVA-test. P-value < 0.05 was statistically significance

Supplemental Table 5. Medication adherence by MMAS-8 items and pill counts at baseline and follow-up assessment points

	Baseline			Follow-up		
	Control group N = 105 n (%)	Intervention group N = 105 n (%)	*P*-value	Control group N = 89 n (%)	Intervention group N = 91 n (%)	*P*-value[*]
MMAS-8 items			0.70			<0.01
Low adherence (<60%)	9 (8.6%)	6 (5.7%)		3 (3.4%)	0 (0.0%)	
Medium adherence (60 to <80%)	48 (45.7%)	48 (45.7%)		36 (40.4%)	18 (19.8%)	
High adherence (80 to 100%)	48 (45.7%)	51 (48.6%)		50 (56.2%)	73 (80.2%)	
Pill counts			0.35			0.01
Low adherence (<60%)	7 (6.7%)	13 (12.4%)		11 (12.4%)	4 (4.4%)	
Medium adherence (60 to <80%)	13 (12.4%)	16 (15.2%)		15 (16.9%)	5 (5.5%)	
High adherence (80 to 100%)	85 (81.0%)	76 (72.4%)		63 (70.8%)	82 (90.1%)	

[*]Analysis conducted by ANOVA-test. *P*-value <0.05 was statistically significance.

Supplemental Table 6. Medication adherence (MMAS-8 items scale and Pill counts) of control and intervention groups

Medication adherence	Control group Mean ± SD	Intervention group Mean ± SD	*P*-value[*]
Baseline	N = 105	N = 105	
MMAS-8 items (scores)	7.1 ± 1.1	7.2 ± 1.0	0.46
Pill counts (%)	89.2 ± 17.8	87.8 ± 17.9	0.59
Follow-up	N = 89	N = 91	
MMAS-8 items (scores)	7.3 ± 0.9	7.7 ± 0.6	<0.01
Pill counts (%)	86.1 ± 17.0	91.6 ± 12.3	0.01

[*]Analysis conducted by independent student *t*-test. *P*-value <0.05 was statistically significance.