Adherence to triple-component antihypertensive regimens is higher with single-pill than equivalent two-pill regimens: A randomized controlled trial

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Abstract

Using a single-pill combination (SPC) for hypertension (HTN) treatment resulted in better adherence and persistence than a free-equivalent combination in previous observational studies. The aim of this study is to confirm superior adherence with a triple-component SPC compared with an equivalent two-pill regimen in a randomized controlled trial (RCT) using a medication event monitoring system (MEMS). This is a multicenter, open-label, RCT. Subjects were persons with HTN whose clinic blood pressure was not adequately controlled (systolic >140 mmHg or diastolic >90 mmHg) with a dual combination. Eligible patients were randomized to either the triple-component SPC (olmesartan/amlodipine/hydrochlorothiazide 20/5/12.5 mg) group or the equivalent two-pill (olmesartan/hydrochlorothiazide 20/12.5 mg + amlodipine 5 mg) group and maintained for 12 weeks. Primary outcomes were the difference in percentage of doses taken (PDT) and percentage of days with the prescribed dose taken correctly (PDTc) between the single- and two-pill therapy groups, calculated from MEMS data. From 8 hospitals, 145 patients with HTN were randomized. The single-pill group had significantly higher PDT and PDTc than the two-pill group: median (25–75 percentile) PDT 95.1 (86.7–100.0) versus 92.1 (73.0–97.3); and PDTc 91.0 (79.4–96.5) versus 88.6 (69.2–96.3%), $P = 0.04$ for both by the Wilcoxon rank sum test. The single-pill combination of the triple-component antihypertensive regimen showed better adherence than the equivalent two-pill therapy. Reducing pill burden by means of a single-pill combination is an effective strategy for enhancing adherence to multiple-agent antihypertensive therapy.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Previous studies suggested that the use of a single-pill combination (SPC) in hypertension (HTN) treatment produced better adherence and persistence than a free-equivalent combination. However, supportive data are confined to dual-component SPC and came from observational studies using medication possession ratio as an outcome.

WHAT QUESTION DID THIS STUDY ADDRESS?
The objective of this study is to investigate whether a triple-component SPC improved medication adherence over an equivalent two-pill combination therapy in a randomized controlled trial using medication event monitoring systems.
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Medication adherence in the SPC group was superior to that of two-pill group, confirming previous findings from observational studies.
HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
This finding strongly supports the current HTN treatment guideline to prefer SPC with a higher level of evidence.

INTRODUCTION

Adherence to and persistence of treatment is an important but occasionally neglected issue in hypertension (HTN) management.[1] Adherence to pharmacological therapy is known to vary with the clinical setting and patient groups.[2,3] Poor adherence to antihypertensive medication is associated with cardiovascular mortality and hospitalization.[4]

Although various research methods have been used to measure adherence, such as home visits, pill counts, pharmacy records, and drug assays, the medication event monitoring system (MEMS), which is a specially designed medicine container that records the date and time of its opening and from which data can be transferred to a computer and analyzed later, has been considered the gold standard for long-term measurement of medication adherence.[5]

The simplicity of a regimen is known to be an important determining factor in adherence, and in a meta-analysis the use of a single-pill combination (SPC) in HTN treatment produced better adherence and persistence than a free-equivalent combination and also produced lower all-cause health care costs.[6]

However, those data are mostly limited to dual-component SPCs; no study has yet been done on the adherence benefit of a triple-component SPC. Studies on medication adherence are commonly conducted on an observational basis; randomized controlled trials (RCTs) have been rare. Moreover, the medication possession ratio has often been used as the adherence outcome. No study using MEMS-measured adherence parameters as the outcome has been done to investigate the adherence superiority conferred by SPC.

The objective of this study is to use an MEMS to investigate whether a triple-component SPC improved medication adherence over an equivalent two-pill combination therapy.

METHODS

Subjects and study design

This study was an open-label, multicenter, parallel group, RCT: Adherence Measured by Medication Event Monitoring System in Triple Antihypertensive Combination: single- versus two-pill regimen (acronym AMTRAC, registered in the ISRCTN registry, https://doi.org/10.1186/ISRCTN51756760). The study was terminated prematurely due to reaching the statistically significant difference in primary outcome and practical difficulty of further enrollment. The subjects were patients with HTN who needed a triple antihypertensive combination of an angiotensin receptor blocker (ARB) + a calcium channel blocker (CCB) + a thiazide diuretic.

Inclusion criteria:

Patients with HTN whose clinic blood pressure (BP; defined below) was systolic greater than 140 mmHg or diastolic greater than 90 mmHg who had been on dual-component therapy for at least 4 weeks with one of the following combinations in either SPC or free-equivalent combination in a dose equivalent to olmesartan 20 mg or amlodipine 5 mg or hydrochlorothiazide 12.5 mg/day.

1. ARB + CCB
2. ARB + thiazide diuretic
3. CCB + thiazide diuretic.

Exclusion criteria:

1. Severe HTN (baseline clinic systolic BP (SBP) greater than 180 mmHg or diastolic BP greater than 110 mmHg)
2. Suspicion of secondary HTN or any other severe target organ damage or hypertensive emergency necessitating urgent BP control
3. History of intolerance or existing contraindication to CCB, ARB, or thiazide diuretic
4. Medical conditions likely to produce a regimen change, such as recent (within 6 months) major cardiovascular events
5. Cases with severe comorbidities, including severe hepatic or renal insufficiency and dementia with a significant problem in taking regular medications
6. Pregnancy or planning for pregnancy
7. Failure to consent.

The following medications were prohibited during the whole study period:

1. Any antihypertensive agents except the study drugs
2. Vasodilators that can affect BP, including nitrates.

Eligible patients were randomized either to one-pill (triple-component SPC, olmesartan/amlodipine/hydrochlorothiazide 20/5/12.5 mg) or two-pill (dual-component SPC + one free pill: olmesartan/hydrochlorothiazide 20/12.5 mg + amlodipine 5 mg) and maintained for 12 weeks (Figure 1). Each participating hospital performed randomization according to its own predistributed randomization table generated by statistical software (R version 3.6.2, with blockrand package; R Foundation for Statistical Computing, Vienna, Austria) with block randomization (block size = 4) and without stratification for covariates. The physicians or research assistants who initiated the enrollment process had no prior knowledge of the allocation details before randomization. After randomization, blinding was not possible because of the inherent nature of the study.

Medications were dispensed in MEMS (MEMS V TrackCap; Aardex, Ltd., Zug, Switzerland) that each contained one set of pills. Thus, the one-pill group received one container, and the two-pill group received two containers for the entire study period. At the end of the study, the MEMS were collected, and the data were transferred to a computer and analyzed by Powerview V (Aardex, Ltd.). If a patient dropped out after randomization for any reason, the case was included in the final analysis so long as the MEMS was returned and its data were retrievable.

This study complies with the Declaration of Helsinki and was approved by the institutional review board of each hospital where study subjects were enrolled, including Samsung Medical Center (Seoul, Republic of Korea). Informed consents were obtained from the enrolled subjects.
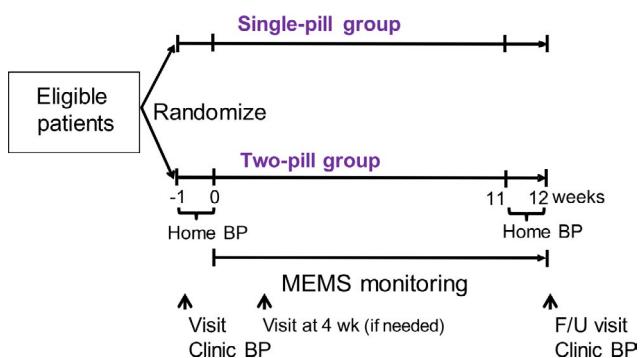

FIGURE 1 Study design. Single-pill group: triple-component SPC: olmesartan + amlodipine + HCTH, 5/20/12/5 mg. Two-pill group: dual-component SPC (olmesartan + HCTH, 20/12.5 mg) + amlodipine 5 mg. BP, blood pressure; HCTH, hydrochlorothiazide; MEMS, medication event monitoring system; SPC, single-pill combination

Blood pressure measurements

At the initial visit, manual BP measurement was done by the auscultatory method. The procedure was as follows: BP measurements were done in a quiet room by a single research nurse. After patients had been sitting quietly for at least 5 min, BP was measured 3 times at 1-min intervals with the arm resting on the desktop. If the discrepancy in the SBP between the first and last measurements exceeded 20 mmHg, an additional measurement was done, and the first reading was discarded. An average of three measurements was used. BPs were obtained from both arms, and when the difference in the SBP between the arms was greater than 10 mmHg, the arm with the higher SBP was used for further measurements; otherwise, the patient's nondominant arm was used. BPs taken in an upright position at 1 and 5 min were obtained at the first visit.

Home BP monitoring was done during two 1-week periods. The first was immediately after randomization while the patients continued with their previous medication for 1 week, and then the assigned medication and MEMS monitoring was started. The second monitoring period was during the 12th week. The protocol was as follows: after the patient took a 5-min rest in a seated position, 2 measurements were done at 1 min intervals in the morning before drug intake (6–10 a.m.) and in the evening (6–10 p.m.) with a designated monitor (HEM-7120; Omron, Kyoto, Japan), and the results were recorded by the patients. Measurements on the other days or other timings were not prohibited. The averages of all valid measurements for each 1-week period were used in the analyses.

Primary and secondary outcomes

Primary outcomes:

Difference in the percentage of doses taken (PDT) and percentage of days on which the prescribed dose was taken correctly (PDTc) between single-pill therapy and two-pill therapy.

PDT and PDTc were calculated as follows:

$$PDT = \frac{Number\ of\ doses\ taken}{Number\ of\ prescribed\ doses} \times 100\%$$

$$PDTc = \frac{Number\ of\ days\ meds\ were\ taken\ correctly\ as\ prescribed}{Number\ of\ prescribed\ days} \times 100\%$$

For example, in the single-pill therapy group, the number of prescribed doses would be 1×12 weeks $\times 7 = 84$ tablets. If 70 of 84 tablets were taken, the PDT would be $70/84 \times 100 = 83.3\%$. If the number of days with 1 pill per day taken correctly was 66 days of 84 days, PDTc

would be 66/84 * 100 = 78.6%. In the two-pill therapy group, the number of prescribed doses would be 2 × 12 weeks × 7 = 168 tablets. If 140 of 168 tablets were taken, the PDT = 140/168 × 100 = 83.3%. If the number of days with two pills per day taken correctly was 60 of 84 days, the PDTc would be 60/84 × 100 = 71.4%. Note that the denominator is the number of prescribed doses in PDT and the number of prescribed days in PDTc.

The instruction for the patients was taking medication in the morning irrespective of the breakfast and one pill a day for one-pill group and two pills together once a day for two-pill group. If a patient does not conform to the prescription on a certain day (i.e., not taking or taking more than once the medication of the day or taking only one pill in two-pill group), that day does not count in the PDTc. Timing of medication and whether two pills were taken together or separately was not considered in determining nonadherence.

Secondary outcomes:

Difference in the proportion of PDT and PDTc greater than or equal to 80% in each period[7]
Difference in clinic SBP between single- and two-pill therapy.

Statistical analyses

Sample size estimation was difficult due to the absence of a similar study. The initially estimated sample size was 300, with a significance level of 0.05 (2-sided), statistical power of 0.8, minimal detectable difference of 5% points, and a within-individual SD of 14%. In a meta-analysis of observational studies comparing adherence between SPC and a free-equivalent combination of 2 pills, the difference in the medication possession ratio between the two groups was in the range of 6.6%–22.5% in 7 studies. A minimal detectable difference of 5% was thus used as a conservative estimate because overall adherence is expected to increase in an RCT setting, thereby diluting the difference. In previous Korean data, the SD of PDT in 80 patients with HTN receiving monotherapy was 14%.[8] Although that is not a within- but between-individual SD, it is the only previously available Korean data. Overall, the estimated total sample size of 300 is conservative.

Normally distributed continuous variables are reported as means and SDs, and all other variables are reported as medians and interquartile ranges. Proportions are reported as both a percentage and actual numbers. Because the distribution of PDT and PDTc was skewed and deviated from the normal distribution, the difference between the single-pill and two-pill regimens was tested using the Wilcoxon rank-sum test. The differences of proportions were tested by the

χ^2 test. Because the main purpose of the study is to show the superiority of SPC and covariates were assumed to be mostly balanced by randomization, multivariate analysis was not considered to be mandatory. However, because adverse events were different between the groups additional analysis using multiple logistic regression using PDT greater than or equal to 80% as an outcome variable was done. All statistical analyses were performed in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline clinical characteristics

The process for screening, enrollment, and randomization is shown in Figure 2. A total of 145 patients from 8 university or tertiary-care hospitals were randomized from March 2016 to August 2018. The baseline clinical characteristics are shown in Table 1. The mean age was the mid-50s, and more men than women were enrolled (M:F = 65:35%). The mean duration of HTN was 8.6 years, and only a small proportion (9%) of patients had a HTN duration of less than 1 year. Other baseline clinical characteristics, such as number of concomitant medications, baseline clinic BP, body mass index, and lifestyle factors (smoking, etc.) did not differ between the groups. The data from 132 patients whose MEMS were retrievable and parameters for the primary outcomes could be calculated were analyzed to determine differences in outcomes.

Primary and secondary outcomes

As shown in Table 2, the primary outcomes (PDT and PDTc) significantly favored the single-pill group over the two-pill group. Although the median values of PDT and PDTc showed only moderate differences, patients with low adherence were apparently more prevalent in the two-pill group, as shown in Figure 3.

The secondary outcomes showed mixed results. The proportion of good PDT and PDTc (≥80%) both showed a tendency toward higher values in the single-pill group, but only PDT reached statistical significance. A post hoc analysis for the differences in proportion of very low adherence (PDT and PDTc ≤30%) patients between the two groups showed that the proportion of PDT less than or equal to 30% tended to be higher in the two-pill group than the single-pill group, but the difference was not significant (4.5% vs. 0%, p by Fisher's exact test = 0.24). The proportion of PDTc less than or equal to 30% was significantly higher in the two-pill compared to the single-pill group (10.7% vs. 0%, p by Fisher's exact test = 0.01).

FIGURE 2 CONSORT flow diagram of the study. Reasons for exclusion from randomization: declined to participate (*n* = 2), not meeting inclusion criteria (*n* = 1). Reason for exclusion from analysis: failed to retrieve MEMS (*n* = 5 and 8 for single- and two-pill groups, respectively). CONSORT, consolidated standards of reporting trials; MEMS, medication event monitoring system
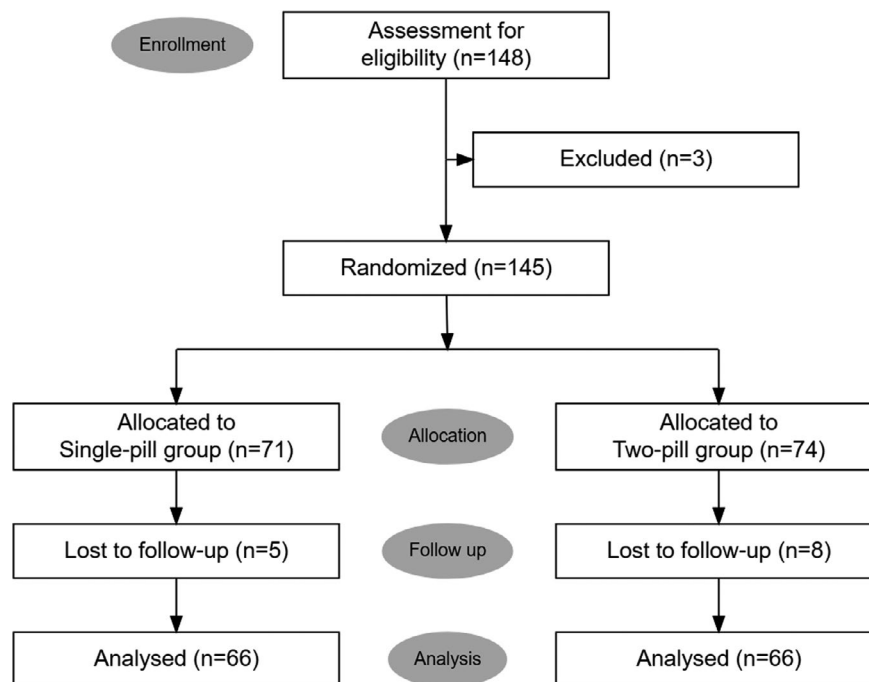

TABLE 1 Baseline clinical characteristics

Variables	Total	Single-pill group	Two-pill group	*p* value[*]
N	145	71	74	
Age, years	56.0 ± 15.3 (137)	55.1 ± 15.8 (68)	56.8 ± 14.8 (69)	0.53
Female, %	34.7 (50/144)	35.2 (25/71)	34.2 (25/73)	1.00
Duration of HTN, years	8.6 (3.4–15.0) (131)	8.0 (3.4–16.1) (64)	9.0 (3.6–15.0) (67)	0.91
Baseline SBP, mmHg	147.8 ± 9.6 (145)	148.3 ± 9.2 (71)	147.2 ± 10.1 (74)	0.51
Baseline DBP, mmHg	92.1 ± 10.2 (145)	91.8 ± 10.6 (71)	92.3 ± 9.9 (74)	0.81
BMI, kg/m^2	27.3 ± 4.0 (145)	27.3 ± 4.2 (71)	27.3 ± 3.8 (74)	0.96
Current smoking, %	15.2 (22/145)	11.3 (8/71)	18.9 (14/74)	0.29
Exercise ≥3×/week, %	29.9 (43/144)	34.3 (24/70)	25.7 (19/74)	0.34
Alcohol intake ≥3×/week, %	20.7 (30/145)	14.1 (10/71)	27.0 (20/74)	0.09
Any adverse events, %	40.0 (58/145)	43.7 (31/71)	36.5 (27/74)	0.48
Drug-related adverse reaction , %	16.6 (24/145)	23.9 (17/71)	9.5 (7/74)	**<0.05**
Early termination (%)	12.4 (18/145)	11.3 (8/71)	13.5 (10/74)	0.87

Bold indicates the statistical significant values.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HTN, hypertension; SBP, systolic blood pressure.

*The *p* value between single-pill and two-pill groups.

Both in-clinic and home BP measurements, especially SBP, tended to decrease more in the single-pill group than the two-pill group, but that difference was not statistically significant (Table 2).

Multiple logistic regression with PDT greater than or equal to 80% as the outcome variable showed that using SPC is a significant predictor of better adherence (odd ratio 3.63, 95% confidence interval 1.32–9.96) after adjustment for age, gender, concomitant medications, and drug-related side effects. Patients with concomitant medications greater than or equal to 3 is more likely to have PDT greater than or equal

to 80%(odd ratio 6.65, 95% confidence interval 1.44–30.73). Other covariates were statistically insignificant.

Adverse events

The total number of adverse events and the proportion of early termination did not differ significantly between the single-pill and two-pill groups. However, drug-related adverse reactions were reported in 24 patients and were significantly more prevalent in the single-pill group (Table 1).

TABLE 2 Primary and secondary outcomes according to the groups

Outcomes	Single-pill group (n)	Two-pill group (n)	p value
PDT, %	95.1 (86.7–100.0) (66)	92.1 (73.0–97.3) (66)	**<0.05**
PDTc, %	91.0 (79.4–96.5) (66)	88.6 (69.2–96.3) (66)	**<0.05**
PDT ≥80%, %	84.8 (56/66)	68.2 (45/66)	**<0.05**
PDTc ≥80%, %	72.7 (48/66)	59.1 (39/66)	0.14
Clinic SBP change, mmHg	−19.3 ± 15.3 (63)	−17.2 ± 15.1 (64)	0.44
Clinic DBP change, mmHg	−11.7 ± 9.6 (63)	−10.6 ± 9.4 (64)	0.49
Home SBP change, mmHg	−14.0 ± 10.8 (32)	−11.8 ± 12.8 (31)	0.46
Home DBP change, mmHg	−7.1 ± 6.6 (31)	−7.1 ± 7.4 (30)	0.98

Notes: Bold indicates the statistical significant values.

PDT and PDTc are shown as the median (25–75 percentile), and the differences were tested using the Wilcoxon rank sum test. Differences in proportions were tested by the χ^2 test, and the differences in blood pressure reductions (shown as mean ± SD) by *t*-test.

Abbreviations: DBP, diastolic blood pressure; PDT, percentage of doses taken; PDTc, percentage of days with prescribed dose taken correctly; SBP, systolic blood pressure.
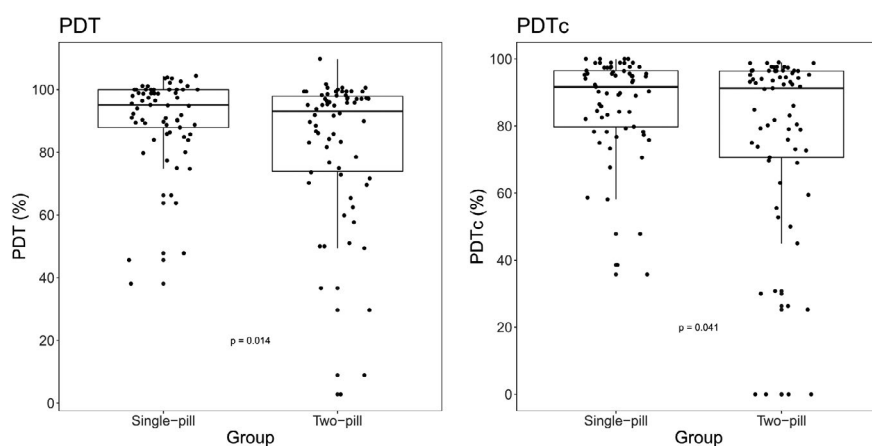

FIGURE 3 Primary outcomes (PDT and PDTc). PDT, percentage of doses taken; PDTc, percentage of days with prescribed dose taken correctly

Among patients who reported an adverse drug-related reaction, 15 of 17 patients in the single-pill group complained of dizziness or fatigue, and the other 2 experienced palpitations and leg edema, respectively; 5 of 7 patients in the 2-pill group complained of dizziness or weakness, and the other patients reported palpitations and diplopia. Most of the patients graded their adverse events as "mild" in severity, except for two subjects who graded it as "moderate." Among the patients who terminated the follow-up prematurely, the reasons for dropout were drug-related adverse effects in 2 of 8 patients in the single-pill group and 2 of 10 in the 2-pill group, which was not a significant difference.

Adherence parameters tended to be higher in those without drug-related adverse events (PDT 87.1%, PDTc 80.5%) compared wth those with it (PDT 80.8%, PDTc 76.8%) but the differences were not statistically significant (*p* for PDT and PDTc = 0.14 and 0.51, respectively, by Wilcoxon rank-sum test). Differences according to the occurrence of "any" adverse events were negligible (with and without adverse events, PDT 86.8% vs. 84.6%, PDTc 80.1% vs. 79.4%).

Two subjects, both allocated to the single-pill group, experienced serious adverse events during the study. One subject underwent knee surgery due to degenerative joint disease, and the other was admitted and received surgery for acute appendicitis. Both were discharged uneventfully, and neither of those events was considered to be directly related to the clinical trial.

DISCUSSION

This is the first RCT comparing the medication adherence to triple-component SPC and an equivalent two-pill combination using MEMS-measured adherence parameters as the outcome.

Many interventional studies have sought to improve medication adherence and persistence, but they have had mixed results,[9] probably reflecting the complexity of human behavior that determines medication adherence. Among various measures to improve medication adherence, SPC resulted in better adherence and persistence compared with equivalent free combinations with relative consistency in many observational studies.[6] However, those studies generally used the medication possession ratio from pharmacy records, which is convenient and effective in investigating a large population but focuses mainly on persistence, with an inherent limitation in measuring adherence because it is impossible to measure

when and whether the dispensed medication is taken by the patient.

In this RCT, we used MEMS and obtained parameters of adherence such as PDT and PDTc, and we found that SPC had a modest but significant advantage in adherence over the equivalent two-pill regimen. RCTs to investigate the effect of SPC in medication adherence are rare, and no previous RCT used MEMS to measure the adherence parameters.[10] One Japanese trial[11] reported no difference in adherence between dual-component SPC and an equivalent free combination, but that study used pill counts as the adherence parameter.

The difference in adherence between the two groups in our study was apparently modest, showing only a small difference in median values. However, the main difference was in the low-adherence group. Fewer patients in the single-pill group showed low adherence than in the two-pill group. Several patients in the 2-pill group had 0% PDTc because they completely neglected 1 of the 2 containers. The exact cause of this phenomenon is unclear and can only be speculated. Probably patients with relatively higher motivation to pharmacological treatment may not be hindered by the number of pills, whereas those with lower motivation and thus with lower adherence may be more influenced by whether it is a one-pill or two-pill regimen.

Although medication adherence is an important practical issue in HTN management, as well as in many other chronic conditions, few interventional studies show actual improvement in clinical outcomes.[12] A recent trial showed that an intervention to improve medication adherence resulted in only modest increase (9% point) without statistical significance.[13] Considering the results of this study and the overall difficulty and complexity of improving adherence, using SPC is a simple, easy, and feasible measure to improve medication adherence. It has already been recommended by the major guidelines,[14,15] and this study provides a higher level of supporting evidence for those recommendations.

Previous studies on the adherence benefit of SPC were done mainly with dual-component SPC. However, many patients with HTN need triple combination therapy,[16] and this study provides convincing evidence that triple-component SPC has superiority over an equivalent two-pill regimen as well.

In terms of BP lowering effect, a meta-analysis showed only an insignificant trend favoring SPC,[10] consistent with our study finding. However, there remained a possibility that home, rather than clinic BP measurements, would reveal a BP lowering effect with a difference in adherence. Although the home BP change did not differ between groups in our data, the average home SBP at the end of the follow-up period was significantly lower in the SPC group than in the two-pill group (121.0 ± 9.8 vs 126.0 ± 9.1 mmHg, $p = 0.04$, data not shown in the table). Home BP monitoring was done properly by only a little over half of the study subjects, which probably made our power to evaluate BP change inadequate. Adequate home BP monitoring might better reveal the favorable influence of better adherence to BP control. A further study addressing that hypothesis is warranted.

Contrary to the previous study results, those with higher pill-burden (≥3) showed higher adherence. These patients might have higher motivation for medication adherence because of more serious comorbidities or this is possibly another chance finding, considering very wide confidence interval.

Drug-related adverse reaction, mostly dizziness and/or weakness, were more common in the single-pill group. It may be possibly due to more effective BP lowering by SPC, but this is inadequate explanation because the difference in the adherence is small and the difference of BP reduction between the two groups were insignificant. This might be a finding by chance. More attention should be paid to those who were prescribed SPC, because of less flexibility of the dose adjustment. However, severe side effects were rare and only a small number of the subjects actually dropped out due to drug-related adverse reaction.

There is a concern that MEMS monitoring itself can affect adherence. The recognition of monitoring can enhance a patient's motivation to adhere to treatment and dilute the difference between treatment regimens. However, it is practically impossible to hide the purpose of MEMS monitoring from patients. Home BP monitoring could also positively influence adherence. However, many patients with HTN already perform self-monitoring, and it is not practical to prohibit it. One randomized controlled study using MEMS showed that the effect size of home BP monitoring on adherence was small and clinically insignificant.[17] We instructed patients to measure their home BP during the designated periods, but we did not do anything else to specifically enhance medication adherence.

In a study investigating a multidrug regimen with MEMS, each drug should be dispensed in a separate MEMS container to prevent contamination and patient confusion. Therefore, two MEMS containers were used for the two-pill group in this study. However, recently multidose drug dispensing (MDD), which provides patients with disposable bags containing all the drugs intended for each dosing moment, has been suggested as a tool to improve medication adherence.[18,19] Whether MDD is comparable to SPC in adherence benefit is another research question that cannot be answered with our data. Further study on this issue is needed.

Another limitation of the study is that it was prematurely terminated and the number of enrollments reached only about half of the designated goal. Although there were

significant differences in the primary outcomes, the sample size may be inadequate to test the differences in secondary outcomes.

In conclusion, a triple-component single-pill combination was superior in medication adherence to an equivalent two-pill regimen. Previous findings from observational studies that pill burden is an important determinant in adherence were confirmed by this RCT using a medication event monitoring system.

CONFLICT OF INTERESTS

AUTHOR CONTRIBUTIONS

J.S. wrote the manuscript. J.S., K.T.A., B-R. C., S.Y.L., B.J.K., D.K.K., J-I.P., and W-S.L. designed the research. J.S., K.T.A., B-R.C., S.Y.L., B.J.K., D.K.K., J-I. P., and W-S.L. performed the research. J.S. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.