

Impact of antihypertensive medication adherence on blood pressure control in hypertension: the COMFORT study

K. MATSUMURA¹, H. ARIMA², M. TOMINAGA³, T. OHTSUBO¹, T. SASAGURI⁴, K. FUJII⁵, M. FUKUHARA⁶, K. UEZONO⁷, Y. MORINAGA¹, Y. OHTA⁸, T. OTONARI⁹, J. KAWASAKI¹⁰, I. KATO¹¹, T. TSUCHIHASHI⁸ and THE COMFORT INVESTIGATORS

From the ¹Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka, Japan, ²The George Institute for Global Health, University of Sydney, Level 10, King George V building, Missenden Road, Sydney, Australia, ³Division of Cardiology, Kyushu Central Hospital, Shiobaru 3-23-1, Minami-ku, Fukuoka, Japan, ⁴Department of Clinical Pharmacology, Kyushu University, Fukuoka, Japan, ⁵Division of Internal Medicine, Imazu Red Cross Hospital, Imazu 377, Nishi-ku, Fukuoka, Japan, ⁶Department of Environmental Medicine, Kyushu University, Fukuoka, Japan, ⁷Institute of Health Science, Kyushu University, Fukuoka, Japan, ⁸Division of Hypertension, National Kyushu Medical Center, Jigyohama 1-8-1, Chuo-ku, Fukuoka, Japan, ⁹Otonari Clinic, Murasaki 3-6-28, Chikushino, Fukuoka, Japan, ¹⁰Kawasaki Cardiovascular Clinic, Kashiihama 3-2-1, Higashi-ku, Fukuoka, Japan and ¹¹Kato Clinic, Torikai 5-4-12, Johnan-ku, Fukuoka, Japan

Address correspondence to Dr K. Matsumura, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. email: matsumk@intmed2.med.kyushu-u.ac.jp

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Summary

Background: It has not been fully elucidated whether antihypertensive medication adherence affects blood pressure (BP) control in hypertension cases.

Aim: To investigate the association of adherence to antihypertensive drug regimens and BP control using data from the Combination Pill of Losartan Potassium and Hydrochlorothiazide for Improvement of Medication Compliance Trial (COMFORT) study.

Design: An observational analysis from a randomized controlled trial.

Methods: A total of 203 hypertensive subjects were randomly assigned to a daily regimen of a combination pill (losartan 50 mg/hydrochlorothiazide 12.5 mg) or two pills, an angiotensin II receptor blocker and a thiazide diuretic. Medication adherence calculated based on pill counts and BPs was evaluated at 1, 3 and 6 months after randomization.

Results: The subjects were divided into three groups according to their adherence, i.e. relatively low-adherence (<90%; $n=19$), moderate-adherence (90–99%; $n=71$) and high-adherence (100%; $n=113$) groups. Clinical characteristics of the subjects including BP, sex, randomized treatments and past medical history did not differ significantly among the three groups. Achieved follow-up BPs over the 6-month treatment period, which were adjusted for age, sex, baseline BP and randomized treatment, were significantly higher in the low-adherence group (135/78 mmHg) compared with the high-adherence (130/74 mmHg; $P=0.02/0.02$) and the moderate-adherence (128/74 mmHg; $P=0.003/0.02$) groups.

Conclusions: Low adherence to an antihypertensive-drug regimen was associated with poor BP control.

Introduction

Many clinical trials have indicated that strict control of blood pressure (BP) using antihypertensive drugs is important to prevent cardiovascular disease in patients with hypertension.¹ Thus, the guidelines for managing hypertension have recommended lower BP levels as targets.^{2–4} BP control has been improving in the past decades; however, it has been shown that a large portion of hypertensive subjects have still failed to achieve adequate BP levels.^{5–8}

Control of BP depends on many factors, such as age, clinical features and doses or classes of antihypertensive drugs used for treatment.^{9–11} Medication adherence has also been considered one of the important factors involved in the control of BP,¹¹ although it has not been fully investigated, especially in Japan. Moreover, it has been shown that high adherence to antihypertensive medications was associated with a decreased risk of acute cardiovascular events,¹² which might be attributable to the extended reduction of BP; however, changes in BP were not investigated in that study.

The Combination Pill of Losartan Potassium and Hydrochlorothiazide for Improvement of Medication Adherence Trial (COMFORT) was an investigator-oriented, multicenter, open, randomized controlled trial carried out in 29 hospitals and clinics in Japan.¹³ The COMFORT study was originally designed to investigate whether antihypertensive treatment with a single pill combining antihypertensive drugs would improve medication adherence and BP control. The main results have been reported previously.¹³ Based on the previous findings, the hypothesis of this study was that good medication adherence would achieve lower BP levels, independent of whether the patients took the combination pill or combined treatment with two antihypertensive drugs. Here, we investigated the impact of medication adherence on BP control using data from the COMFORT study.

Methods

Participants

The detailed protocol of the COMFORT study and its main results have been described previously.¹³ Briefly, 207 patients with hypertension (≥ 20 years old) who tolerated the combination therapy of a standard dose of an angiotensin II receptor blocker (ARB; losartan 50 mg, candesartan 8 mg, valsartan 80 mg, telmisartan 40 mg or olmesartan 20 mg) and a small dose of a diuretic (thiazides or related sulphonamide compounds; hydrochlorothiazide 6.25–12.5 mg, trichlormethiazide 0.5–1 mg or

indapamide 0.5–1 mg) were randomly assigned to the combination pill group or the control group. Patients assigned to the former received a combination pill (losartan 50 mg/hydrochlorothiazide 12.5 mg), and those assigned to the latter received an ARB and a diuretic.

After excluding four patients who lacked values for their adherence rate, a total of 203 patients were included in this analysis. The study protocol was approved by the Ethics Committee for Human Studies at Kyushu University and/or by the appropriate ethics committee at each participating site, and the procedures followed were in accordance with the International Conference on Harmonization of Good Clinical Practice guidelines. Written informed consent was obtained from all patients prior to registration.

Procedures

Participants were seen at 1, 3 and 6 months after randomization. At each visit, medication adherence was evaluated by counting the number of residual pills that the patients had failed to take. Adherence rates were calculated for each visit using the following formula: adherence rate (%) = [(number of prescribed pills – number of residual pills)/number of prescribed pills] \times 100. According to the worst medication adherence in the treatment periods of 0–1, 1–3 or 3–6 months, the subjects were divided into three groups, namely, relatively low-adherence (<90%), moderate-adherence (90–99%) and high-adherence (100%) groups. At each visit, BPs were also measured twice in a sitting position using a standard sphygmomanometer after resting for at least 5 min. The mean of the two measurements at each visit was used in this analysis.

Statistical analysis

Baseline characteristics among the groups were analyzed with analysis of variance (ANOVA) for continuous variables or with the chi-square test for categorical variables. The effects of adherence on follow-up BP were assessed by a linear mixed model using follow-up BP as the repeated measures, and including age, sex, baseline BP, use of calcium channel blockers and randomized treatment as covariates. $P < 0.05$ was considered statistically significant. These analyses were performed using the SAS system for Windows (release 9.2, SAS Institute).

Results

Table 1 summarizes the baseline characteristics of the three groups of patients divided by adherence

Table 1 Baseline characteristics by adherence rate

	Adherence rate			<i>P</i> -value
	<90% (<i>n</i> = 19)	90–99% (<i>n</i> = 71)	100% (<i>n</i> = 113)	
Age (years)	62 (12)	60 (13)	66 (10)	0.01
Female	8 (44)	27 (38)	56 (50)	0.26
Medical history				
Stroke	1 (5)	2 (3)	4 (4)	0.89
Coronary heart disease ^a	0 (0)	0 (0)	2 (2)	0.25
Other cardiovascular disease	0 (0)	1 (1)	6 (5)	0.11
Diabetes	3 (16)	4 (6)	14 (12)	0.66
Dyslipidemia	9 (47)	38 (54)	60 (53)	0.76
Hyperuricemia	3 (16)	18 (25)	32 (28)	0.28
Current smoker	4 (21)	9 (13)	16 (14)	0.65
Current drinker	11 (58)	42 (59)	57 (50)	0.29
Drug use				
Antihypertensive therapy				
ACE inhibitor	0 (0)	0 (0)	0 (0)	–
ARB	19 (100)	70 (100)	111 (98)	0.25
Thiazides or related sulphonamide compounds	17 (89)	64 (93)	96 (86)	0.34
Other diuretic	0 (0)	2 (3)	10 (9)	0.05
Calcium channel blocker	3 (16)	23 (33)	60 (53)	0.0003
α -blocker	0 (0)	6 (9)	9 (8)	0.42
β -blocker	0 (0)	8 (12)	9 (8)	0.69
Other	0 (0)	3 (4)	0 (0)	0.22
Antidiabetic therapy	0 (0)	3 (4)	10 (9)	0.08
Lipid-lowering therapy	4 (21)	18 (26)	33 (29)	0.45
Urate-lowering therapy	1 (5)	3 (4)	8 (7)	0.54
Antiplatelet therapy	2 (11)	3 (4)	13 (12)	0.34
Oral anticoagulant	0 (0)	1 (1)	6 (5)	0.12
Clinical features				
SBP (mmHg)	138 (18)	134 (12)	134 (13)	0.46
DBP (mmHg)	80 (12)	78 (10)	76 (11)	0.09
Pulse rate (per min)	70 (11)	71 (8)	69 (10)	0.58
Hematocrit (%)	42 (5)	42 (5)	41 (5)	0.37
Serum creatinine (mg/dl)	0.75 (0.18)	0.79 (0.19)	0.84 (0.47)	0.50
Serum sodium (mmol/l)	141 (2)	141 (2)	141 (2)	0.45
Serum potassium (mmol/l)	4.1 (0.4)	4.1 (0.4)	4.3 (0.5)	0.06
Serum uric acid (mg/dl)	5.8 (1.4)	6.1 (1.3)	6.0 (1.4)	0.76
Study treatment				
Combination pill	9 (47)	37 (52)	56 (50)	0.96

ACE, angiotensin converting enzyme.

After excluding four patients with missing value on adherence, 203 were included. Adherence rate = worst in periods of 0–1, 1–3 or 3–6 months. Data are mean (SD), median (IQR) or *n* (%). *P* values were estimated using ANOVA or chi-square test.

^aMyocardial infarction or coronary revascularization.

rate. No significant difference was found among the three groups for any variable except for age ($P=0.01$) and antihypertensive therapy using calcium channel blocker ($P=0.0003$).

Table 2 shows the achieved follow-up BPs that were adjusted for age, sex, baseline BP, use of calcium channel blocker and randomized treatment. Mean systolic BP (SBP) and diastolic BP (DBP) over the 6-month period were significantly higher in the relatively low-adherence group (<90%;

135.2/78.3 mmHg) compared with the high-adherence (100%; 130.0/74.4 mmHg; $P=0.02/0.02$) and the moderate-adherence (128.3/74.4 mmHg; $P=0.003/0.02$) groups.

Discussion

In this study, we have prospectively investigated the effect of medication adherence on BP control in

Table 2 Achieved follow-up BP by adherence rate

	Follow-up BP				Overall difference	P-value ^a
	1 month	3 months	6 months	Overall ^a	Mean difference, mmHg (95% CI) ^a	
SBP						
Adherence rate 100%	130.0 mmHg	129.5 mmHg	131.1 mmHg	130.0 mmHg	Reference	
Adherence rate 90–99%	128.0 mmHg	128.7 mmHg	127.9 mmHg	128.3 mmHg	−1.7 mmHg (−4.5 to 1.0)	0.21
Adherence rate <90%	134.8 mmHg	138.9 mmHg	135.1 mmHg	135.2 mmHg	5.2 mmHg (0.7–9.6)	0.02
DBP						
Adherence rate 100%	72.9 mmHg	73.7 mmHg	73.0 mmHg	74.4 mmHg	Reference	
Adherence rate 90–99%	76.7 mmHg	76.7 mmHg	75.4 mmHg	74.4 mmHg	0.1 mmHg (−1.9 to 2.0)	0.94
Adherence rate <90%	78.4 mmHg	82.3 mmHg	82.4 mmHg	78.3 mmHg	4.0 mmHg (0.8–7.2)	0.02

CI, confidence interval.

^aAdjusted for age, sex, baseline BP, use of calcium channel blockers and randomized treatment.

Japanese hypertensive subjects using the data of COMFORT study. The principal findings of this study were that BP control was dependent on medication adherence, even though medication adherence for antihypertensive drugs was quite excellent in this group of Japanese hypertensive subjects. To the best of our knowledge, this study is the first to demonstrate prospectively the impact of medication adherence on BP control in hypertensive subjects in Japan.

Hypertension is still one of the important risk factors for cardiovascular disease¹⁴; therefore, guidelines for the treatment of hypertension require adequate reduction of BP.^{2–4} Control of BP has been improving in the past decades, but many cases of hypertension remain insufficiently controlled for BP, even in the USA and Japan.^{6–8} In Japan, adequate control of office BP (<140/90 mmHg) was achieved in only 42% of patients <50 years old.⁵ In the USA, the National Health and Nutrition Examination Survey 2009–10 demonstrated that only 47% of all hypertensive people and 60% of treated hypertensive people had BP controlled to the level of <140/90 mmHg.⁷ To achieve adequate control of BP, combination therapy and strategies to maintain good medication adherence are proposed to be important issues, especially in the treatment of resistant hypertension.¹¹

In this study, subjects with a relatively low-adherence rate (<90%) showed significantly higher BP compared with those with a perfect adherence rate (100%) over a 6-month treatment period. It had been controversial whether medication adherence is associated with BP control.¹⁵ One of the reasons why this relationship has not been clearly established is the difficulty of evaluating medication adherence. The methods to evaluate medication

adherence are generally classified into three categories: subjective (e.g. patient interview), direct (e.g. measurement of drug concentrations in the blood) and indirect (e.g. pill counts, prescription refills, electronic monitoring of medication use).¹⁶ Based on this study's results, the pill-count method appears to have worked appropriately.

Mazzaglia *et al.*¹² have demonstrated that a high-adherence rate to antihypertensive treatment was associated with a reduction in cardiovascular events among newly diagnosed hypertensive patients. They did not provide BP data during the treatment; however, it is likely that a reduction of cardiovascular events was mediated, at least in part, by a larger reduction in BP associated with appropriate use of antihypertensive drugs. In this study, mean SBP and DBP over 6 months were significantly higher in the relatively low-adherence group compared with the high-adherence group. Based on the previous and present findings, it could be suggested that patient adherence to antihypertensive drug regimens is important for preventing future cardiovascular events as well as to obtaining better control of BP in hypertension.

This study was limited by the fact that numbers of the subjects included and the follow-up period of 6 months might not have been enough. In addition, the medication adherence rates were unexpectedly high. The precise reason for these high adherence rates is not obvious. However, the medical insurance system in Japan may have been a factor. Since all Japanese people are covered by public medical insurance systems by more than 70%, the out-of-pocket medical expense for drugs is relatively inexpensive in Japan compared with other countries. Another possible reason for the high-adherence rate is the selection bias of the patients

participating in this study, because all patients were screened for run-in periods. Patients with low-adherence rates might have been excluded. Therefore, it seems difficult to apply the findings of this study to general Japanese hypertensive patients. Many participants were not newly diagnosed hypertensive patients, but rather had been treated with antihypertensive drugs for several years.¹⁷ Furthermore, it has been demonstrated that merely participating in a clinical trial significantly increases adherence.¹⁸ Even considering these limitations, however, the present findings are largely new, because this is the first study to prospectively examine the impact of medication adherence on BP control in Japan. Further studies with more subjects and longer observational periods will be needed to establish evidence of a relationship among medication adherence, BP and cardiovascular events.

In conclusion, this study has evaluated the impact of adherence to an antihypertensive drug regimen on BP control over a 6-month period. Reduction of BP was found to be dependent on the medication adherence rate, despite the overall high-adherence rates of the subject groups. It will be important for physicians to develop strategies to improve medication adherence such as patient education, cost reduction of drugs, good communication, etc., for further reduction of cardiovascular events among hypertensive patients.¹⁹

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COMFORT Committees and Investigators

Steering committee: Kiyoshi Matsumura (chair), Takuya Tsuchihashi, Toshiyuki Sasaguri, Koji Fujii, Mitsuhiro Tominaga, Toshio Ohtsubo, Masayo Fukuhara and Hisatomi Arima.

Data and safety monitoring committee: Keiko Uezono and Hiromi Muratani.

Investigators: Kiyoshi Matsumura, Takuya Tsuchihashi, Toshiyuki Sasaguri, Koji Fujii, Mitsuhiro Tominaga, Toshio Ohtsubo, Masayo Fukuhara, Hisatomi Arima, Yuko Ohta, Takatoshi Otonari, Junya Kawasaki, Yuki Morinaga, Shuntaro Kagiya, Tetsuhiko Nagao, Isao Kato, Yae Fujishima, Kimika Arakawa, Yuji Fukudome, Uran Onaka, Kenichi Goto, Yoshito Nakamura, Junpei Yamada, Kenichi Sugi, Koichi Arase, Toshiharu Kawadoko, Shin Nakamura, Keiichi Midorikawa, Kensuke Nomiyama, Toshihiko Hashimoto, Atsushi Murakami, Koichi Fukuda, Toshimitsu Soh, Akihiko Eshita and Morioki Ishibashi.

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