

Effects of Switching from Treatment with Amlodipine and Atorvastatin Using Two Pills to an Equal Dose of Single-Pill Therapy in Japanese Outpatients

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This study examined whether switching from amlodipine and atorvastatin treatment using two pills to an equal dose of single-pill therapy is useful in Japanese outpatients. We retrospectively reviewed data obtained from 94 outpatients for whom treatment with two pills, namely amlodipine and atorvastatin, was switched to an equal dose of single-pill therapy in 11 hospitals. The criterion for enrollment in this study was that patients had switched their medication without changing other anti-hypertensive or anti-cholesterol drugs. Neither systolic nor diastolic blood pressure changed significantly after switching to an equal dose of single-pill therapy, whereas low-density lipoprotein (LDL) cholesterol levels significantly decreased after the medication was switched from 94 ± 24 mg/dl to 89 ± 17 mg/dl ($p=0.015$). A switch from medication with two separate pills of amlodipine and atorvastatin to an equal dose of single-pill therapy resulted in an overall decrease in LDL cholesterol. The results indicated that the switch to single-pill therapy might be a useful treatment.

Key words: hypertension, dyslipidemia, single-pill therapy

In Japan, the prevalence of lifestyle-related illnesses such as hypertension and dyslipidemia is high, and the two conditions are often seen in combination. The use of antihypertensive medications or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has become fundamental therapy in the management of patients with hypertension or dyslipidemia to prevent future cardiovascular events [1,2]. In general, chronic disease management requires the use of multiple medications, and the majority of patients are on two or more medications for optimal treatment.

Although a compound-pill therapy of amlodipine-atorvastatin is available for patients with hypertension and dyslipidemia, there are very few reports concerning the benefits of this single-pill therapy for concomitant

hypertension and dyslipidemia [3].

The purpose of this study was to determine whether switching from treatment with amlodipine and atorvastatin using 2 pills to an equivalent treatment using a single pill would be useful in Japanese outpatients.

Materials and Methods

Subjects. We retrospectively reviewed data obtained from 94 outpatients for whom treatment with amlodipine and atorvastatin using two pills was switched to an equal dose of single-pill therapy (Caduet®) in 11 hospitals (Aki General Hospital, Chikamori Hospital, Hosogi Hospital, Japanese Red Cross Kochi Hospital, Kochi Prefectural Hata Kenmin Hospital, Kohoku Hospital, Niyodo Hospital, Ooida Hospital, Susaki

Kurosio Hospital, Tosa Municipal Hospital, and Kochi Medical School Hospital) from January 2010 to December 2013. The criteria for enrollment in this study were patients who switched to single-pill therapy that dispensed an equivalent amount of medication without changing other antihypertensive or anticholesterol drugs and who underwent serial daytime blood pressure measurements in an outpatient clinic or serial blood examinations for cholesterol values within at least 12 months before and after switching medications. A total of 94 patients were enrolled as the subjects of this study. The study was approved by the Ethics Committee on Medical Research of Kochi Medical School Hospital (ERB-100411).

Clinical evaluation. Evaluation of the patients included obtaining a medical history, blood pressure measurements, laboratory data (total cholesterol and low-density lipoprotein (LDL) cholesterol), and detailed questions about the prescription and the actual conditions under which they took their medicine. We assessed the changes in blood pressure values and cholesterol levels from the baseline to the first evaluation after the medications were switched. To evaluate the factors responsible for lowering LDL cholesterol levels, the patients were divided into 2 groups. Patients whose LDL cholesterol levels were lower than before they switched medications were classified as having lowered LDL cholesterol levels. Patients whose LDL cholesterol levels were the same as or higher than before switching medications were classified as not having lowered LDL cholesterol levels.

Data analysis. All data are expressed as means \pm SD or frequencies (percentages). Differences in continuous variables were assessed using Student's *t*-test. Pearson's chi-square test was used for comparisons between non-continuous variables, and Fisher's exact test was used when the expected frequency was lower than 5. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SPSS (version 14.0J) statistical software (SPSS Inc., Chicago, IL, USA).

Results

Study population. The data for 94 outpatients with a mean age of 72 ± 10 years were retrospectively analyzed. About half of the patients (51%) were men. Thirty-six patients had diabetes mellitus, 34 had coronary heart disease, and 21 had a history of stroke. Most

patients ($n=89$) were treated with Caduet[®] #4 (amlodipine at 5 mg/day and atorvastatin at 10 mg/day), while 1 patient was treated with Caduet[®] #1 (amlodipine at 2.5 mg/day and atorvastatin at 5 mg/day), 3 patients were treated with Caduet[®] #2 (amlodipine at 2.5 mg/day and atorvastatin at 10 mg/day) and 1 patient was treated with Caduet[®] #3 (amlodipine at 5 mg/day and atorvastatin at 5 mg/day).

Changes in blood pressure and cholesterol values.

Figure 1A shows the changes in blood pressure in 86 of the 94 patients during a follow-up period of 71 ± 45 days. Neither systolic nor diastolic blood pressure changed significantly after switching to an equal dose of single-pill therapy. As shown in Fig. 1B, although the total cholesterol levels only changed from 175 ± 34 mg/dl to 171 ± 24 mg/dl ($p=0.231$) ($n=66$, follow-up period of 159 ± 105 days), the LDL cholesterol levels significantly decreased after switching from 94 ± 24 mg/dl to 89 ± 17 mg/dl of medication ($p=0.015$) ($n=78$, follow-up period of 160 ± 106 days).

Factors responsible for lowering LDL cholesterol levels. As shown in Table 1, the patients with lowered LDL cholesterol levels were younger than the patients without lowered levels. There were fewer diabetes mellitus patients in the group with lowered LDL cholesterol levels.

Figure 2 shows the distribution of ages and changes in LDL cholesterol levels after switching to an equal dose of single-pill therapy. There seemed to be different patterns among the different age groups (middle age, elderly, and very elderly). Figure 3 shows the changes in LDL cholesterol levels for the patients < 60 years old ($n=12$; Fig. 3A), 60-74 years old ($n=34$; Fig. 3B) and ≥ 75 years old ($n=32$; Fig. 3C). The LDL cholesterol levels significantly decreased in patients aged < 60 years and patients aged ≥ 75 years old. On the other hand, patients aged 60-74 years did not show significant changes in LDL cholesterol levels.

When the patients were divided into 2 groups, namely those with and without diabetes mellitus, the LDL cholesterol levels were significantly decreased in the patients without diabetes mellitus ($n=48$) from 97 ± 21 mg/dl to 89 ± 16 mg/dl ($p < 0.01$), whereas the levels in the patients with diabetes mellitus ($n=29$) only changed from 89 ± 30 mg/dl to 88 ± 20 mg/dl ($p=0.802$) (Figs. 4A and 4B).

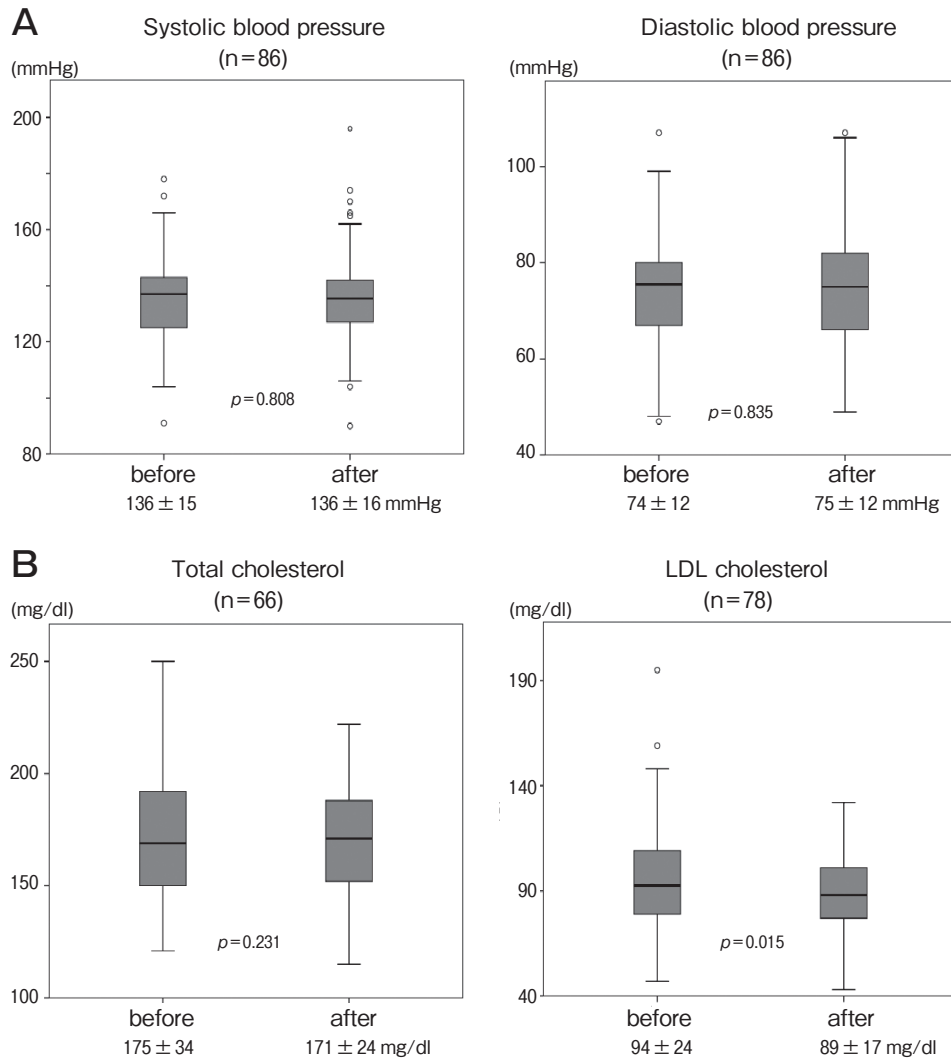


Fig. 1 The changes in blood pressure (A) and cholesterol (B). Data are shown as means \pm SD.

Table 1 Factors responsible for lowering LDL cholesterol levels after switching the medication

	Patients without lowered LDL levels (n = 29)	Patients with lowered LDL levels (n = 49)	p-value
Sex: Male, n	12 (41%)	27 (55%)	0.241
Age, years	75 \pm 9	70 \pm 1	0.034
75 \leq years old, n	13 (45%)	19 (39%)	0.599
Prescription dates, days	52 \pm 20	52 \pm 20	0.965
The kinds number of medications, n	6 \pm 3	6 \pm 3	0.576
The timing for taking statin: morning, n	19 (66%)	27 (55%)	0.422
Diabetes mellitus, n	15 (52%)	14 (29%)	0.048
Coronary heart disease, n	13 (45%)	15 (31%)	0.230
History of stroke, n	5 (17%)	8 (16%)	1.000

Data are shown as the means \pm standard deviation or number (%). LDL, low-density lipoprotein.

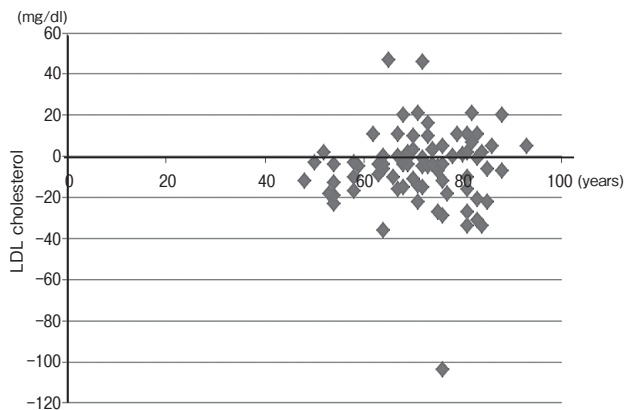


Fig. 2 The distribution of ages and changes in LDL cholesterol levels.

Discussion

The aim of this study was to determine whether switching from treatment with amlodipine and atorvastatin using 2 pills to an equal dose of single-pill therapy is useful for the treatment of patients without consideration of bias due to the efficacy of the medication.

In this study, there was no significant change in systolic or diastolic blood pressure after the therapy was switched. This is thought to be because the patients monitored their blood pressure at home and had obtained information on high blood pressure from various sources, and were thus knowledgeable about hypertension and motivated to take the medication.

On the other hand, LDL cholesterol levels decreased

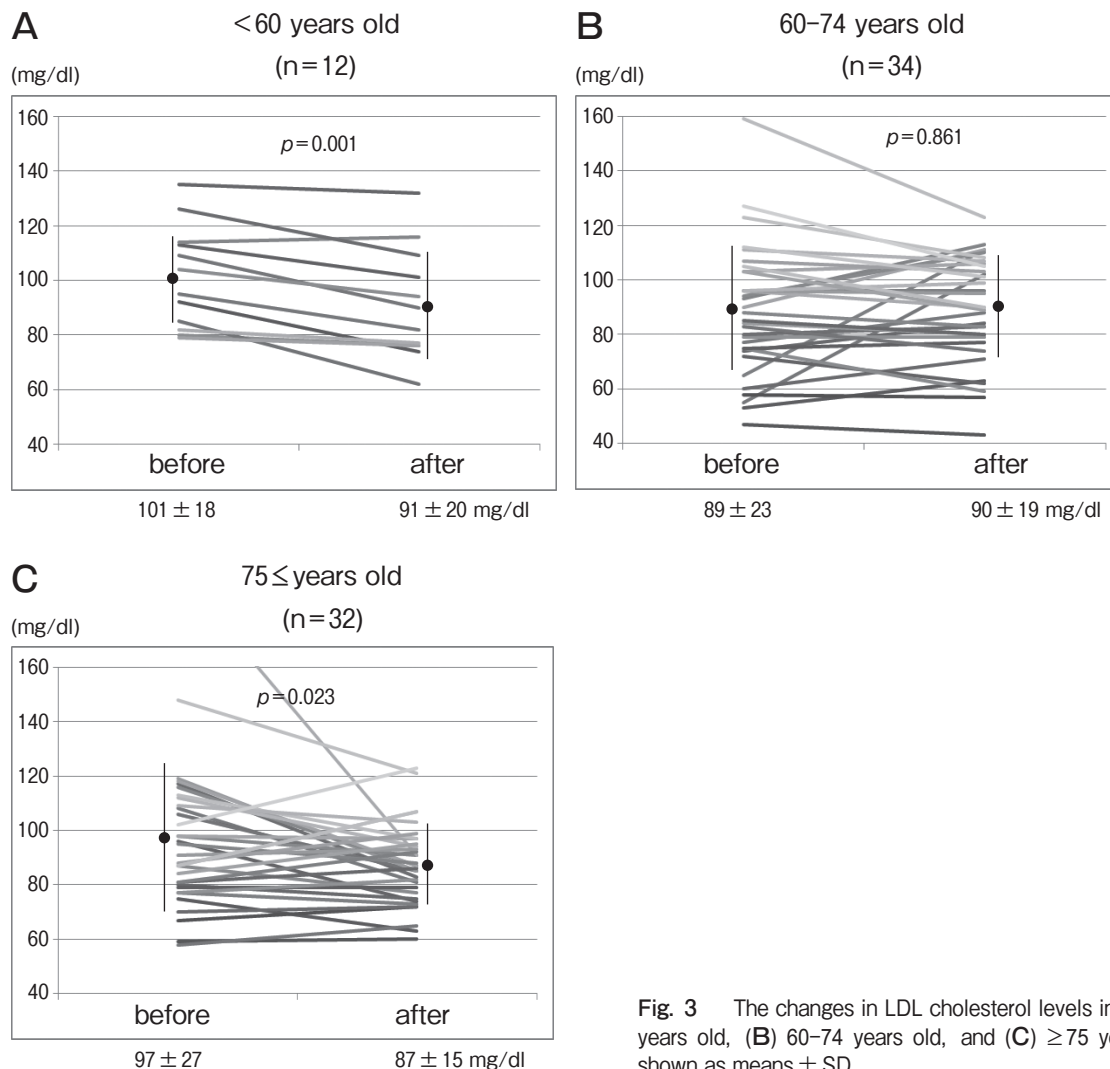


Fig. 3 The changes in LDL cholesterol levels in patients (A) <60 years old, (B) 60–74 years old, and (C) ≥ 75 years old. Data are shown as means \pm SD.

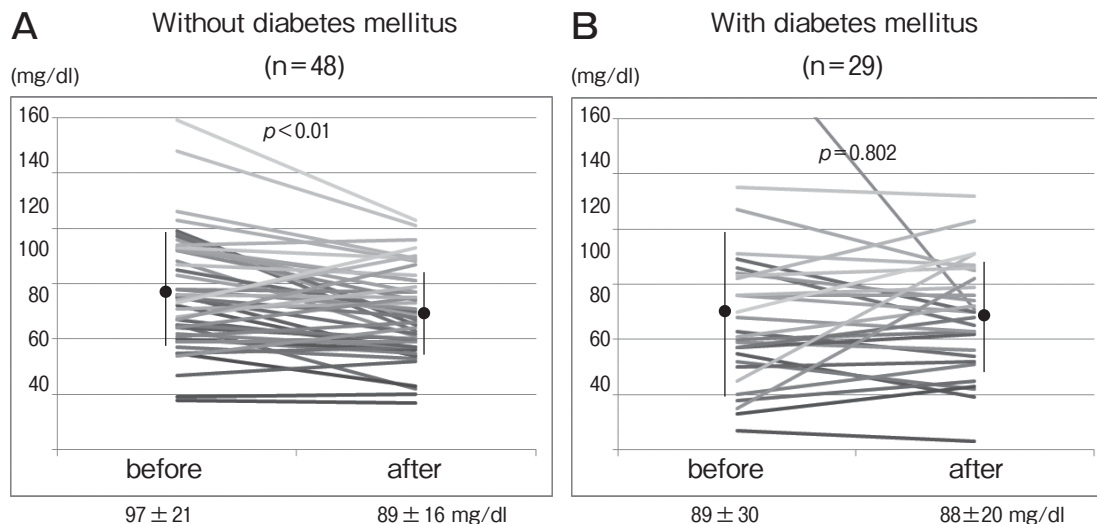


Fig. 4 The changes in LDL cholesterol levels in patients (A) without diabetes mellitus and (B) with diabetes mellitus. Data are shown as means \pm SD.

significantly after the medication was switched. Although we did not assess medication adherence in this study, these results might have been caused by an improvement in adherence to the medication. A previous study reported that adherence to anti-dyslipidemia drugs is poor [4]. Although the precise reason for this is unclear, it might be that patients have no subjective symptoms, and cholesterol levels cannot be easily measured by patients themselves like blood pressure levels [5-7]. Polypharmacy and the complexity of the treatment regimen are known to be important determinants of poor medication adherence [8]. Ellis *et al.* reported that younger age (less than 65 years) was one of the factors associated with nonadherent behavior in patients treated with a statin [9]. Thus, the switch to single-pill therapy might have improved the adherence to medication in our subjects.

Moreover, our study showed that LDL cholesterol levels decreased significantly in patients without diabetes mellitus but not in patients with diabetes mellitus. Although it has been reported that adherence to medication decreases in patients with diabetes mellitus [10, 11], in our study we speculated that patients with diabetes mellitus, like patients with hypertension, recognized their disease and were highly aware of the need to prevent future cardiovascular events, and thus might have shown good adherence to their medication regimen.

In our study, the kinds of and number of medica-

tions used before switching were not factors that reduced the LDL cholesterol level after the switch to single-pill therapy. The timing with which the statins were taken (for example, after breakfast or after dinner) was also not a factor in reducing the LDL cholesterol level. Patients tend to disregard the importance of statins compared to other medications such as antihypertensive drugs and drugs for diabetes, and the fact that the LDL cholesterol level decreased after switching to single-pill therapy suggests that switching the medication improved adherence.

In this study, no additional dietary and/or physical therapy instructions were given other than the directive to switch therapies. In other words, this study was a retrospective study in which the only intervention was the switching of drugs. Teramoto *et al.* reported the necessity of diet therapy for patients with dyslipidemia regardless of whether LDL-C lowering drugs are prescribed [12]. The effects of low- and moderate-intensity exercise on LDL levels should not be ignored, because low- to moderate-aerobic exercise intensities have shown a positive effect on LDL subfractions [13]. Therefore, different results might be obtained if dietary and/or physical therapy were combined with the switching of medications.

While our study could have some significant benefits, it also has some limitations. First, it was a retrospective study conducted in a small number of hospitals. A multivariate analysis was not used to evaluate

the factors responsible for lowering LDL cholesterol levels because of the small sample numbers. Second, some data such as data on triglycerides, non-high-density lipoprotein cholesterol (non-HDL), and serum lipid levels were not obtained. Elevated non-HDL levels are a significant risk factor for the development of atherothrombotic infarction as well as coronary heart diseases, but they reduce the risk of cardioembolic infarction in the general Japanese population [14]. Third, medication adherence was not assessed by an objective index such as the proportion of days covered, and cognitive function in the elderly patients was not assessed in this study. Finally, some reports have shown that statins increase the risk of new-onset diabetes mellitus in a dose-dependent manner [15, 16]. We consider new diabetes mellitus onset due to statins to be an adverse event requiring considerable attention. However, this study did not analyze if there were any changes in HbA1c after statin adherence was improved.

In conclusion, a switch from treatment with amlodipine and atorvastatin using two separate pills to an equal dose of single-pill therapy resulted in an overall decrease in LDL cholesterol. The results suggested that the switch to single-pill therapy might be a useful treatment.

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