Hypcholesterolemia and hypertension are well-known risk factors for coronary artery disease (CAD). Thus, many drugs have been developed to lower serum cholesterol and blood pressure (BP), and have been used in clinical practice over the years. Such drugs not only successfully lower serum cholesterol and BP, but many clinical trials have also shown that they are effective in reducing the risk for cardiovascular disease (CVD).\(^1\)\(^-\)\(^7\) However, it was also found that despite multiple pharmacological interventions, significant residual cardiovascular risk remains in patients with CVD.\(^8\) In fact, in an observational study we conducted, in which patients who had undergone coronary angiography and had ≥75% stenosis according to the American Heart Association (AHA) guideline\(^9\) in at least one coronary artery, we found that the incident rate of cardiovascular events was approximately 62.8 per 1,000 patient-years, a much higher

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incident rate than that for the general Japanese population. Recently, several clinical trials have shown that intensive lowering of low-density lipoprotein cholesterol (LDL-C) results in further risk reduction for patients at high risk of CVD or those already with CVD. Several clinical guidelines for hypertension therapy recommend vigorous antihypertensive treatment in patients with higher risk for CVD. In this context, we designed a study to evaluate the efficacies of intensive lowering of both BP and LDL-C, compared with conventional therapy, for reducing cardiovascular events in Japanese patients with CAD.

Methods

Trial Design
JCADII was a multicenter, randomized, open label, blinded-endpoint trial. The details of the study rationale and design were published previously. Patient flow is shown in Figure 1. The trial was approved by the institutional ethics committee of each participating center and all patients provided written informed consent.

Study Population
Hypertensive and hypercholesterolemic patients who were between 20 and 79 years of age with significant stenosis in at least one major coronary artery were eligible to participate. Significant stenosis of the coronary artery was defined as ≥75% stenosis according to AHA guideline. Hypercholesterolemia was defined as a serum total cholesterol concentration ≥220 mg/dl in the past or during current therapy with statins and/or fibrates. Hypertension was defined as systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg in the past or during current therapy with antihypertensive agents. Major exclusion criteria included known allergic reaction to the study drugs; familial hypercholesterolemia; uncontrolled hypercholesterolemia (serum LDL-C concentration remains ≥180 mg/dl despite conventional therapy); uncontrolled hypertension (SBP remains ≥180 mmHg and/or DBP ≥110 mmHg despite conventional therapy); myocardial infarction (MI) or stroke within the past 3 months; secondary hypertension; and secondary hyperlipidemia (diabetes mellitus-induced hyperlipidemia was not excluded).

Study Procedures
All eligible patients were allocated randomly to either the conventional therapy or intensive therapy (IT) group. Randomization was performed according to the minimization method with the following leveling factors: SBP, serum LDL-C concentration, diabetes mellitus and congestive heart failure. The therapeutic targets for patients assigned to conventional therapy were SBP<140 mmHg and DBP<90 mmHg for hypertension, and serum LDL-C concentration <100 mg/dl for hypercholesterolemia. If the patient had diabetes mellitus, the therapeutic targets for hypertension were SBP<130 mmHg and DBP<80 mmHg, according to Japanese guidelines for hypertension therapy. The therapeutic targets for patients assigned to IT were SBP<120 mmHg and DBP<80 mmHg, according to Japanese guidelines for hypertension therapy. Antihypertensive therapy should have included angiotensin receptor blockers (ARBs), candesartan and/or losartan. Antihypercholesterolemia therapy should have included statins: pravastatin, simvastatin, or atorvastatin. A no drug regimen was allowed if the targets were accomplished with non-pharmacological therapy. Additional therapies were allowed to achieve the target BP and LDL-C concentration, although ARBs and statins not specified above, and angiotensin-converting enzyme inhibitors, were not allowed to be used.
Outcome Measures
The primary endpoint was a composite of all deaths, non-fatal MI, cases of unstable angina pectoris, coronary artery bypass graft surgery, non-fatal stroke, non-fatal major vascular disease and peripheral artery disease. Secondary endpoints included the following: the occurrence of any primary event; all-cause hospitalization; hospitalization because of congestive heart failure; percutaneous coronary intervention; transient ischemic attack; and the composite of the events specified above. Other endpoints included BP; pulse wave velocity; concentrations of serum lipid, high-sensitivity C-reactive protein and B-type natriuretic peptide; left ventricular hypertrophy; and safety.

Statistical Analysis
Based on the JCAD study results,10 we estimated that the annual event rate for cardiovascular events and mortality for patients with CAD would be approximately 6%. Taken together with the results from the Steno-2 study,19 the JCADII study was designed to detect a 41% relative risk reduction in the cardiovascular incidence rate in patients receiving IT, with a 2-sided α level of 0.05 and an 80% detection rate. Assuming a drop-out rate of 2%, the number of patients needed was 250 for each group. Wilcoxon’s test was used for comparison of continuous variables and a χ² test for categorical variables. Survival analyses were performed on the basis of the time to the first event according to the intention-to-treat principle. Survival curves were plotted by the Kaplan-Meier method and hazard ratios were calculated by univariate Cox regression analysis. All reported P values are 2-sided. Analyses were performed using SAS version 9.1.3 software (SAS Institute Inc, Cary, NC, USA).

Shortly before the pre-specified trial end date of 31 October 2010, an interim efficacy analysis was performed according to the protocol because fewer than expected events were observed. The independent data and safety monitoring board voted to recommend termination of the trial according to the results on 18 October 2010. The steering committee accepted

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the 2 Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional therapy</strong> (n=254)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex, male</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Smoker</td>
</tr>
<tr>
<td>DM</td>
</tr>
</tbody>
</table>

History of:
- MI | 59.6% (152) | 60.8% (149) | 0.783 |
- Angina pectoris | 51.0% (130) | 52.7% (129) | 0.708 |
- PCI | 75.7% (193) | 76.7% (188) | 0.783 |
- Coronary bypass surgery | 12.9% (33) | 11.8% (29) | 0.708 |
- Congestive heart failure | 7.1% (18) | 6.1% (15) | 0.673 |
- Ischemic stroke | 3.9% (10) | 5.7% (14) | 0.349 |
- Hemorrhagic stroke | 1.2% (3) | 0.4% (1) | 0.260 |
- Transient ischemic attack | 0.8% (2) | 0.8% (2) | 0.376 |
- Major vascular event | 2.0% (5) | 2.0% (5) | 0.248 |
- Peripheral vascular event | 2.0% (5) | 3.7% (9) | 0.246 |
- SBP (mmHg) | 129.5±16.4 (247) | 130.4±18.5 (234) | 0.532 |
- DBP (mmHg) | 74.2±11.5 (247) | 74.3±12.2 (234) | 0.898 |
- Pulse rate (beats/min) | 69.7±11.4 (207) | 69.6±10.9 (193) | 0.919 |
- Total cholesterol (mg/dl) | 176.5±32.8 (190) | 181.7±27.9 (187) | 0.026 |
- LDL-C (mg/dl) | 98±24.8 (245) | 102.5±24.8 (234) | 0.066 |
- HDL-C (mg/dl) | 54.4±15.2 (243) | 52.5±12.8 (234) | 0.312 |
- Triglyceride (mg/dl) | 142.4±147.7 (246) | 143.4±85.7 (234) | 0.359 |
- CK (I/U/L) | 128.6±78.9 (207) | 121.4±79.7 (204) | 0.149 |
- Uric acid (mg/dl) | 5.9±1.4 (227) | 5.9±1.2 (218) | 0.618 |
- Fasting blood glucose (mg/dl) | 116.1±29.2 (189) | 119.2±33.3 (183) | 0.546 |
- Hemoglobin A₁c (%) | 6.1±1.2 (188) | 6.1±1.2 (185) | 0.967 |
- BNP (pg/ml) | 53±59.6 (179) | 64±79.2 (178) | 0.140 |
- Serum creatinine (mg/dl) | 0.9±0.24 (230) | 0.9±0.27 (218) | 0.381 |
- IVSth | 9.8±2.14 (204) | 9.6±2.05 (194) | 0.421 |
- EF | 59.1±12.0 (206) | 59.4±11.8 (193) | 0.730 |

For dichotomous values, the ratio followed by the actual number is shown. For continuous variables, means±1SD followed by the number of patients is shown. P values for dichotomous variables were calculated using the chi-square test. P values for continuous variables were calculated using the Kruskal-Wallis test.

BMI, body mass index; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CK, creatinine kinase; BNP, B-type natriuretic peptide; IVSth, interventricular septal thickness; EF, ejection fraction.
this recommendation and the trial formally ended on 31 October 2010, as pre-specified.

Role of the Funding Source
The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit this paper for publication.

Results

Study Subjects
A total of 512 patients were randomized, after which 14 patients were excluded because they failed to take the study drug (Figure 1). Subjects were recruited over a 1-year period and were followed for a median of 3.2 years, for a total of 1,600 patient-years of observation. A total of 498 patients, 244 in the IT group and 254 in the conventional therapy group, were included in the final analysis; 14 patients in each group were lost to follow-up.

Baseline Data
Patients were well-matched between the 2 groups in terms of sex, age, BP, serum LDL-C concentration, body mass index, past history of CVD and other variables, except for serum total cholesterol concentration (Table 1).

Change in BP
As shown in Figure 2, at 3 months, SBP and DBP had decreased by 3.3/2.0 mmHg in the conventional therapy group and by 5.7/3.4 mmHg in the IT group; at 3 years it had decreased by 2.7/3.4 mmHg in the conventional therapy group and 9.1/6.4 mmHg in the IT group compared with the baseline level. A statistically significant difference between the 2 groups was observed at year 1 and thereafter for SBP, and a statistically significant difference between the 2 groups was observed at year 2 and thereafter for DBP.

Change in LDL-C
Figure 3A shows that, at 3 months, serum LDL-C had decreased by 5.9 mg/dl in the conventional therapy group and by 15.8 mg/dl in the IT group; at 3 years the decrease compared with baseline was 6.0 mg/dl in the conventional therapy group and 23.0 mg/dl in the IT group. A statistically significant difference between the 2 groups was observed at year 1 and thereafter.

Change in HDL-C
No statistical difference was observed between each time point or between the 2 therapy groups for serum HDL-C concentrations (Figure 3B).

Medications
The medication usage is shown in Table 2. The ratio of patients prescribed atorvastatin was 66.7% for the conventional therapy group, and 58.8% for the IT group at baseline. The respective ratios were 69.1% and 81.5% at year 1, and 61.7% and 83.1% at year 3. The use of pravastatin decreased significantly from 25.3% at year 1 to 7.5% at year 3 in the IT
group, but remained unchanged in the conventional therapy group. Candesartan was more likely to be used in the IT group. Although losartan was prescribed less often for patients in the IT group at year 3, it was prescribed more often in combination with hydrochlorothiazide for patients in the IT group.

Endpoints
At the time of study termination, 18 primary cardiovascular events were recorded in the conventional therapy group and 26 events were recorded in the IT group (Table 3). As shown in Table 3 and Figure 4A, the rates for the primary endpoint were 22.1 and 33.1 per 1,000 person-years in the conventional and IT groups, respectively (hazard ratio for IT group 1.53; 95% confidence interval (CI), 0.84–2.8; P=0.164). Al-

Figure 3. Change in serum cholesterol level according to treatment group. †Statistically significant difference was observed at P<0.001. ‡Statistically significant difference was observed at P<0.01. LDL, low-density lipoprotein; HDL, high-density lipoprotein.
though no statistically significant differences were observed for any component of the primary endpoint between the conventional and IT groups, all components tended to occur more often in the IT group, especially stroke (with rates of 1.2 and 6.4 per 1,000 person-years for the conventional and IT group, respectively; hazard ratio for IT group 5.21; 95%CI 0.61–8.43; P=0.132). Figure 4B shows the Kaplan-Meier curve and hazard ratio for the composite of secondary endpoints.

**Discussion**

The main finding of this study was that, contrary to prior expectation, intensive lowering of both BP and LDL-C in Japanese CAD patients with hypertension and hypercholesterolemia provided no beneficial effect in terms of reducing cardiovascular risk. In fact, though statistically insignificant, a tendency for worse outcomes for patients in the intensive treatment group was observed.

Several clinical studies and meta-analyses conducted in Western countries have shown that intensive lowering of LDL-C reduces the incidence rate of CAD and mortality in CAD patients compared with patients provided the usual care.\textsuperscript{11–13,20} This resulted in a guideline targeting an LDL-C level of 70 mg/dl in patients with CAD.\textsuperscript{21} Although no studies evaluating clinical endpoints for the effects of intensive LDL-C lowering have been conducted in Japan, several studies have evaluated the efficacy of intensive LDL-C lowering by evaluating coronary plaque volume using intravascular ultrasound.\textsuperscript{22} One study showed that intensive LDL-C lowering reduces the amount of coronary plaque in acute coronary

### Table 2. Comparison of Medication Usage in the 2 Treatment Groups

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline (n=255), % (n)</th>
<th>Intensive therapy (n=245), % (n)</th>
<th>Conventional therapy (n=236), % (n)</th>
<th>Intensive therapy (n=222), % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>66.7 (170)</td>
<td>58.8 (144)</td>
<td>69.1 (163)</td>
<td>81.5 (181)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>3.9 (10)</td>
<td>8.2 (20)</td>
<td>4.2 (10)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>23.1 (59)</td>
<td>25.3 (62)</td>
<td>23.7 (56)</td>
<td>9.9 (22)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>1.6 (4)</td>
<td>1.6 (4)</td>
<td>2.1 (5)</td>
<td>0.5 (1)</td>
</tr>
<tr>
<td>Candesartan</td>
<td>63.9 (163)</td>
<td>68.6 (168)</td>
<td>66.1 (156)</td>
<td>70.7 (157)</td>
</tr>
<tr>
<td>Losartan</td>
<td>21.6 (55)</td>
<td>18.4 (45)</td>
<td>26.7 (63)</td>
<td>18 (40)</td>
</tr>
<tr>
<td>Losartan-HCTZ</td>
<td>0 (0)</td>
<td>3 (7)</td>
<td>8.1 (18)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>CCB*</td>
<td>43.9 (112)</td>
<td>47.8 (117)</td>
<td>45.8 (108)</td>
<td>59.9 (133)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>14.5 (37)</td>
<td>15.9 (39)</td>
<td>14 (33)</td>
<td>16.2 (36)</td>
</tr>
<tr>
<td>α-blocker</td>
<td>2.4 (6)</td>
<td>1.6 (4)</td>
<td>2.1 (5)</td>
<td>2.3 (5)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>14.9 (38)</td>
<td>12.7 (31)</td>
<td>16.5 (39)</td>
<td>21.2 (47)</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>94.1 (240)</td>
<td>86.9 (213)</td>
<td>97.5 (230)</td>
<td>96.4 (214)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>22.7 (58)</td>
<td>24.5 (60)</td>
<td>19.9 (47)</td>
<td>22.1 (49)</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of the Outcomes of the 2 Treatment Groups

<table>
<thead>
<tr>
<th>Primary composite endpoints</th>
<th>Conventional therapy</th>
<th>Intensive therapy</th>
<th>HR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Components of the primary endpoints</td>
<td>No. of events</td>
<td>Rate per 1,000 person-years</td>
<td>No. of events</td>
<td>Rate per 1,000 person-years</td>
</tr>
<tr>
<td>All-cause death</td>
<td>8</td>
<td>9.8</td>
<td>9</td>
<td>11.5</td>
</tr>
<tr>
<td>AMI</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>3</td>
<td>3.7</td>
<td>6</td>
<td>7.6</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1.2</td>
<td>5</td>
<td>6.4</td>
</tr>
<tr>
<td>Vascular events</td>
<td>4</td>
<td>4.9</td>
<td>4</td>
<td>5.1</td>
</tr>
<tr>
<td>Secondary composite endpoints</td>
<td>86</td>
<td>105.5</td>
<td>95</td>
<td>121</td>
</tr>
<tr>
<td>Components of the secondary endpoints</td>
<td>No. of events</td>
<td>Rate per 1,000 person-years</td>
<td>No. of events</td>
<td>Rate per 1,000 person-years</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>82</td>
<td>100.6</td>
<td>91</td>
<td>115.9</td>
</tr>
<tr>
<td>Congestive HF requiring hospitalization</td>
<td>4</td>
<td>4.9</td>
<td>5</td>
<td>6.4</td>
</tr>
<tr>
<td>PCI</td>
<td>24</td>
<td>29.5</td>
<td>21</td>
<td>26.7</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Not calculated because the number of events for 1 group was zero.

HR, hazard ratio; CI, confidence interval; AMI, acute myocardial infarction. Other abbreviations see in Table 1.
syndrome patients, compared with patients receiving usual therapy. Another study showed that a 38.6% decrease in LDL-C was associated with a 5.1% decrease in coronary plaque volume in stable CAD patients. These results suggest that intensive lowering of LDL-C in Japanese CAD patients may bring about a reduction in the frequency of CAD events.

As for hypertension, recent management guidelines recommend a lower BP target for patients with higher risk for CVD. For example, the target BP level for patients with chronic kidney disease, diabetes mellitus and a history of MI according to JSH 2009 is <130/80 mmHg. However, there is very scant evidence from randomized clinical trials (RCTs) that intensive lowering of BP to below that level, compared with typical lowering regimens, results in better cardiovascular outcomes. In fact, for patients with CAD, the J-curve phenomenon has been noted several times in the past. However, these arguments are based on post-hoc analyses of RCTs that were not designed to evaluate such effects.

Some studies have shown that cardiovascular risk was not raised when the DBP target was <80 mmHg, despite higher values for actually attained DBP. In our study, the mean BP in both groups was already <140/90 mmHg at the time of inclusion, and we aimed for even lower values in the IT group.
in which the attained mean BP was 121.3/67.9 mmHg.

Based on the arguments above concerning lowering of serum LDL-C and BP, and taking into account that patients included in this study were already well-treated at baseline, we can speculate that the reason why a beneficial effect of intensively these 2 factors was not seen in this study is because of the combination of a beneficial effect for one reduction with a detrimental effect for the other on CAD patients whose cardiovascular risk was already substantially ablated. This is reflected in the lower than expected event rate in the study. When we designed the study we expected the event rate to be 6%, but the actual overall rate was approximately 3% (Table 3). In fact, the LDL-C level and BP at baseline (Table 1) in both groups were approximately the value recommended in the latest Japanese guidelines, and evidence-based cardiovascular medical therapy was used from the start (Table 2). However, this reasoning cannot be stated with confidence because the study was not designed to test such a hypothesis.

Several other factors might have caused unexpected results in our study. One is the lower prescription rate of antithrombotics in the IT group at the time of registration, although the difference became statistically non-significant 3 months after the start of the study (data not shown) and its contribution to the overall results is presumed to be not very large. Another is the switching of the prescription of pravastatin, which is a hydrophilic statin, to that of atorvastatin, which is a lipophilic statin, which occurred more frequently in the IT group. A subanalysis of a study conducted on acute MI (AMI) patients showed that hydrophilic statins may be superior to lipophilic statins in AMI patients with total cholesterol concentrations of 180–240 mg/dl in reducing cardiovascular events. This suggests that the worse outcome observed in the IT group in our study was caused by the decreased rate of prescribing a hydrophilic statin and increased prescription of a lipophilic statin. However, as shown in Table S1, the event rates for those who were prescribed only atorvastatin or were switched from pravastatin to atorvastatin were not higher than those who were prescribed only pravastatin, the average LDL-C levels of whom did not change in 3 years (Table S2), thus making this speculation unlikely.

Our findings show that intensively lowering both LDL-C and BP has no effect in reducing cardiovascular risk in already well-treated Japanese CAD patients. Future studies should be designed to test each treatment effect separately.

### Table 4. Adverse Events in the 2 Treatment Groups During the Study Period

<table>
<thead>
<tr>
<th>Adverse event (n ≥2)</th>
<th>Conventional therapy (n=254)</th>
<th>Intensive therapy (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>1.2% (3)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.4% (1)</td>
<td>2.0% (5)</td>
</tr>
<tr>
<td>CK elevation/myalgia</td>
<td>0.8% (2)</td>
<td>1.2% (3)</td>
</tr>
<tr>
<td>Gut ulcer</td>
<td>0.4% (1)</td>
<td>0.4% (1)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.0% (0)</td>
<td>0.8% (2)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>0.4% (1)</td>
<td>0.4% (1)</td>
</tr>
<tr>
<td>Stomach discomfort</td>
<td>0.4% (1)</td>
<td>0.4% (1)</td>
</tr>
<tr>
<td>Worsening of DM</td>
<td>0.8% (2)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Other adverse events</td>
<td>3.1% (8)</td>
<td>6.1% (15)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>7.5% (19)</td>
<td>11.5% (28)</td>
</tr>
</tbody>
</table>

Abbreviations see Table 1.


Supplemental Files

Supplemental File 1
Table S1. Event Rates for Different Patterns of Statin Prescription
Table S2. Change in Average Serum LDL-C Level According to Statin Prescription Pattern

Supplemental File 2
Data S1. Appendix
Please find supplemental file(s); http://dx.doi.org/10.1253/circj.CJ-11-0695