Efficacy of Out-Patient Cardiac Rehabilitation in Low Prognostic Risk Patients After Acute Myocardial Infarction in Primary Intervention Era

Tsukasa Kamakura, MD; Rika Kawakami, MD; Michio Nakanishi, MD; Muneaki Ibuki, MD; Takahiro Ohara, MD; Masanobu Yanase, MD; Naohiko Aihara, MD; Teruo Noguchi, MD; Hiroshi Nonogi, MD; Yoichi Goto, MD

Background: The efficacy of out-patient cardiac rehabilitation (OPCR) in patients with a low prognostic risk after acute myocardial infarction (AMI) is unclear in the recent primary intervention era.

Methods and Results: A total of 637 AMI patients who participated in in-hospital cardiac rehabilitation were divided into 2 groups; low prognostic risk group (n=219; age <65 years, successful reperfusion, Killip class I, peak serum creatine kinase <6,000 U/L, and left ventricular ejection fraction ≥40%) and non-low prognostic risk group (n=418). The prevalence of coronary risk factors (CRF) was compared between the 2 groups. Then, in the low-risk group, the efficacy of OPCR was compared between active OPCR participants (n=52; ≥20 sessions/3 months) and non-active participants (n=60; <6 sessions/3 months). Compared with the non-low prognostic risk group, the low prognostic risk group had a significantly higher prevalence of current smokers (72% vs. 49%, P<0.05) and patients with multiple CRF (3 or more; 49% vs. 39%, P<0.05). Among the low-risk group, active OPCR participants showed a significantly greater improvement in exercise capacity (peak VO₂, P<0.05) and maintained a better CRF profile (total cholesterol, triglyceride and blood pressure, all P<0.05) than inactive participants at 3 months.

Conclusions: Low prognostic risk AMI patients have a higher prevalence of multiple CRF than non-low risk patients. Even in this low risk group, active participation in OPCR is associated with improved exercise capacity and better CRF profile. (Circ J 2011; 75: 315–321)

Key Words: Acute myocardial infarction; Cardiac rehabilitation; Coronary risk factors; Exercise capacity; Low prognostic risk

Cardiac rehabilitation (CR) is a comprehensive intervention including medically supervised exercise training, risk factor control, patient education, and psychosocial counseling. CR has been reported to be effective in improving numerous intermediate endpoints, including exertional ischemic symptoms, overall feelings of wellness, exercise tolerance, and coronary risk factors (CRF) in patients with coronary artery disease (CAD). In addition, recent meta-analyses of randomized studies on the effects of exercise-based CR in patients with CAD have demonstrated a statistically significant reduction in total and cardiac mortality ranging from 20% to 32% in patients undergoing CR compared with those receiving standard medical care. The guidelines from the American College of Cardiology/American Heart Association and Japanese Circulation Society recommend the use of CR after acute myocardial infarction (AMI) as Class I.10–14

Recently, the widespread use of primary percutaneous coronary interventions (PCI) has enabled early ambulation of patients with AMI by reducing acute phase complications, resulting in minimal physical deconditioning. As a result, many AMI patients leave a hospital early without participating in a recovery phase (phase II) out-patient CR (OPCR) program.15 However, the necessity and efficacy of OPCR remain unclear in AMI patients who are anticipated to be at low risk in terms of long-term prognosis (ie, non-elderly, successful reperfusion, absence of heart failure, and preserved left ventricular (LV) systolic function).

Accordingly, the purpose of the present study was to clarify the prevalence of CRF and to determine the efficacy of a 3-month OPCR program in such presumably low prognostic risk patients after AMI.

Received August 12, 2010; revised manuscript received September 29, 2010; accepted October 6, 2010; released online December 14, 2010  Time for primary review: 21 days
Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Research Center, Suita, Japan
Mailing address: Yoichi Goto, MD, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Research Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan  E-mail: ygoto@hsp.ncvc.go.jp
All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
Methods

Patients
We studied a total of 637 consecutive patients with AMI who participated in a recovery phase CR program and underwent cardiopulmonary exercise testing (CPX) at the beginning and end of a 3-month program in our hospital. The patients were divided into 2 groups: a low prognostic risk group and a non-low prognostic risk group. The low prognostic risk group comprised of 219 patients who fulfilled all of the following criteria indicative of favorable prognosis; age under 65 years, successful reperfusion, Killip class I (an indicator of absence of acute phase heart failure), peak serum creatine kinase (CK) <6,000 U/L, LV ejection fraction (LVEF) ≥40%. The remaining 417 patients who did not fulfill 1 or more of the above 5 criteria were referred to as the non-low prognostic risk group.

As the first step of data analysis, the prevalence each of the CRF (hypertension, hyperlipidemia, diabetes mellitus, obesity and smoking habit) was compared between the low prognostic group and the non-low prognostic group.

As the second step, the efficacy of OPCR in AMI patients at low prognostic risk was examined by comparing the data for exercise capacity and CRF between active participants and non-active participants in the low prognostic risk group. Active participants were defined as patients who attended the OPCR sessions at least 20 times in 3 months (ie, approximately >2times/week), and non-active participants were those who attended OPCR less than 6 times in 3 months (ie, approximately <0.5times/week). There were 52 active participants and 60 non-active participants in the low prognostic group. We did not include the remaining 107 patients with intermediate attendance (patients with 6–19 attendances in 3 months) in the analysis, because the effect of OPCR in this patient group was considered to be modest, if any, and inclusion of this group in the analysis would dilute the measurable efficacy of OPCR. A schematic of the study protocol is provided in Figure 1.

CR Program
The CR program began approximately 1 week after AMI and continued after hospital discharge for 3 months. Patients who had angina or evidence of ischemic changes in their electrocardiogram (ECG) at a low level of exercise (walking test), uncontrolled heart failure, and serious arrhythmia were excluded. Program components included supervised exercise sessions (walking, bicycle ergometer and calisthenics) and education, as previously described.16,17 The exercise intensity was determined individually at 50–60% of heart rate reserve (Karvonen’s equation, \( k = 0.5–0.6 \))18,19 or a heart rate of anaerobic threshold (AT) level obtained in a maximal symptom-limited CPX testing or at level 12–13 (‘a little hard’) of the 6–20 scale perceived rating of exercise (original Borg’s scale).20 The exercise program was started with supervised sessions for 2 weeks, followed by home exercise combined with once or twice-a-week supervised sessions for the remaining 10 weeks. Home exercise consisted mainly of brisk walking at a prescribed heart rate for 30 to 60 min, 3–5 times a week.

Patients were encouraged to attend the education classes that were held 4 times a week with lectures on CAD, secondary prevention, diet, smoking cessation, medication, and...
Cardiac Rehabilitation in Low-Risk AMI Patients

physical activities given by physicians, nurses, dieticians, pharmacists and exercise instructors. In addition, all patients received individual counseling on exercise prescription, secondary prevention, and daily life activities by a physician and a nurse at the time of hospital discharge and the end of the 3-month CR program. Patients were scheduled to undergo blood tests at the beginning and the end of the 3-month CR program.

### Table 1. Comparisons of Clinical Characteristics in the Low and Non-Low Prognostic Risk Groups

<table>
<thead>
<tr>
<th></th>
<th>Low-risk group (n=219)</th>
<th>Non-low-risk group (n=418)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±7</td>
<td>65±9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male (%)</td>
<td>88</td>
<td>83</td>
<td>NS</td>
</tr>
<tr>
<td>Killip class ≥II (%)</td>
<td>0</td>
<td>13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak CK (U/L)</td>
<td>2,458±1,444</td>
<td>3,339±2,639</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CK ≥6,000U/L (%)</td>
<td>0</td>
<td>17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unsuccessful reperfusion (%)</td>
<td>0</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>49.1±6.8</td>
<td>44.4±10.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF &lt;40% (%)</td>
<td>0</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>75.7±70.9</td>
<td>209.8±202.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT (%)</td>
<td>57</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>DM/IGT (%)</td>
<td>47</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>HLP (%)</td>
<td>59</td>
<td>49</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>28</td>
<td>27</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>72</td>
<td>49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary risk factors ≥3 (%)</td>
<td>49</td>
<td>39</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 2. Comparisons of Clinical Characteristics in the Low and Non-Low Prognostic Risk Groups

<table>
<thead>
<tr>
<th></th>
<th>Low-risk group (n=219)</th>
<th>Non-low-risk group (n=418)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±7</td>
<td>65±9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Male (%)</td>
<td>88</td>
<td>83</td>
<td>NS</td>
</tr>
<tr>
<td>Killip class ≥II (%)</td>
<td>0</td>
<td>13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Peak CK (U/L)</td>
<td>2,458±1,444</td>
<td>3,339±2,639</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CK ≥6,000U/L (%)</td>
<td>0</td>
<td>17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unsuccessful reperfusion (%)</td>
<td>0</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>49.1±6.8</td>
<td>44.4±10.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEF &lt;40% (%)</td>
<td>0</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>75.7±70.9</td>
<td>209.8±202.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HT (%)</td>
<td>57</td>
<td>56</td>
<td>NS</td>
</tr>
<tr>
<td>DM/IGT (%)</td>
<td>47</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>HLP (%)</td>
<td>59</td>
<td>49</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>28</td>
<td>27</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>72</td>
<td>49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary risk factors ≥3 (%)</td>
<td>49</td>
<td>39</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

CK, serum concentration of creatine kinase; LVEF, left ventricular ejection fraction; BNP, brain natriuretic peptide; HT, hypertension; DM, diabetes mellitus; IGT, impaired glucose tolerance; HLP, hyperlipidemia. Values are mean ± SD.
Patients were scheduled to undergo a symptom-limited CPX at the beginning and the end of the 3-month CR program. After a 2-min rest on the bicycle ergometer in the upright position, the patients started pedaling at an intensity of 0 W for 1 min (warm-up), and then performed an incremental exercise test with a ramp protocol (10 or 15 W/min) until exhaustion. Twelve-lead ECG was continuously monitored and blood pressure (BP) was measured once-a-min with a sphygmomanometer. Expired gas was collected and analyzed continuously with an AE-300S gas analyzer (Minato Co, Osaka, Japan). Peak oxygen uptake (peak VO$_2$) was defined as the highest VO$_2$ value achieved at peak exercise. Ventilation (VE) and carbon dioxide output (VCO$_2$) were measured and the VO$_2$ value at AT or ventilatory threshold was determined as the point at which VCO$_2$ increased in a non-linear fashion relative to the rate of VO$_2$ (according to the VE/VO$_2$ time trend, the respiratory exchange ratio elevation point, or the V-slope method).

Statistical Analysis
Baseline characteristics between the 2 groups were compared using unpaired t-test and chi-square test. Data at baseline and after the 3-month OPCR were compared by paired t-test. A P-value less than 0.05 was considered statistically significant. Data are presented as the mean±standard deviation.

Results
Prevalences of CRF in Low Prognostic Risk Group vs. Non-Low Prognostic Risk Group
Clinical characteristics in the low prognostic risk group and the non-low prognostic risk group are summarized in Table 1. Compared with the non-low prognostic risk group, the low prognostic risk group was on average significantly younger, and did not have heart failure on admission or unsuccessful reperfusion, but had lower peak CK and B-type natriuretic peptide (BNP) concentrations and preserved LVEF. Although these findings were anticipated by the definition of the group, they reconfirm that the patients in the low prognostic group were undoubtedly at low prognostic risk. However, when the prevalence of CRF was compared between the 2 groups, the percentage of patients with dyslipidemia, smoking habit and multiple CRF (equal to or more
than 3) was significantly higher in the low prognostic risk group than in the non-low prognostic risk group.

### Efficacy of OPCR in Low Prognostic Risk Group: Comparison Between Active and Non-Active Participants

Baseline characteristics in active participants and non-active participants in the low prognostic risk group are summarized in Table 2. Although active participants were significantly older than the non-active participants, they were both non-elderly (less than 65 years old). Peak CK was low and LVEF was relatively preserved in both groups. These findings reconfirm that both active and non-active participants are apparently at low prognostic risk. Although there were minor differences in the prevalence of male patients, smokers and β-blocker use, there were no significant differences in exercise capacities at baseline between the 2 groups.

During the 3-month OPCR period, only a few patients experienced changes in medication; statins were introduced in 3 patients (5.8%) in the active participants and 2 patients (3.3%) in the non-active participants, and diuretic medications were started in 2 patients (3.3%) in the non-active participants. Thus, the baseline clinical characteristics of active and non-active participants were almost equivalent, except for the frequency of OPCR attendance.

### Discussion

The major findings of the present study are that the low prognostic risk AMI patients had a higher prevalence of multiple CRF than the non-low prognostic risk patients. Although the finding that younger AMI patients have higher prevalences of smoking and hyperlipidemia than elderly patients is in accordance with previous studies, there has been no report demonstrating higher prevalence of multiple CRF in low prognostic risk AMI patients with successful reperfusion and preserved LVEF. According to TIMI risk score [27] or CADILLAC risk score [28], this finding might appear confusing or counterintuitive. However, from the viewpoint of lifetime CAD risk, this finding might have a significant impact on the long-term prognosis of apparently low prognostic risk AMI patients.

The second major finding in the current study is that active participation in OPCR improved CRF (BP, dyslipidemia, and obesity) and exercise capacity even in the low prognostic risk group. There have been no studies that reported the effect of OPCR in the low prognostic risk AMI patients. Taylor et al [12] reported in a meta-analysis of randomized controlled trials that the effect of OPCR on total mortality did not differ between studies before and after year 1995 (odds ratio 0.84 before 1995 vs. 0.62 after 1995, NS), but they did not assess the effect of OPCR on the low prognostic risk patients after successful reperfusion. Witt et al recently reported that participation in OPCR after AMI was associated with improved survival and reduced recurrent myocardial infarction (MI) at 3 years, but the rate of reperfusion was only 33% in their patients. Squires et al reported that a 3-year coronary disease management program in OPCR for CAD patients was effective in achieving the secondary prevention goals, but their assessment did not target the low prognostic risk patients. Thus, the present study has demonstrated for the first time the favorable effects of OPCR on CRF and exercise capacity in the low prognostic AMI patients.
Clinical Implications
It remains unknown whether the improvements in CRF profiles and exercise capacity achieved by active participation in OPCR can lead to an improved long-term prognosis in the low prognostic risk AMI patients. However, Tani et al reported that successful life style modification with exercise, body weight reduction and smoking cessation for 6 months was associated with coronary plaque volume regression in low prognostic risk CAD patients. Belardinelli et al reported in the ETICA (Exercise Training Intervention after Coronary Angioplasty) trial that a 6-month OPCR for the relatively low risk CAD patients after successful PCI (49% having AMI) reduced cardiac events and hospital re-admission during the follow-up period (33±7 months). In addition, because the magnitude of the improvement in endothelial function afforded by OPCR does not correlate with the improvements in CRF, the general consensus at present is that the favorable effect of OPCR on the long-term prognosis is mediated by a direct anti-atherosclerosis effect of exercise training rather than by improvements in CRF. Therefore, further study is necessary to determine the long term effect of OPCR in AMI patients with low prognostic risk.

In the present study, significant differences were found between active and inactive OPCR participants in BMI, total cholesterol, triglyceride and BP, but not in LDL-C or glucose tolerance. One might argue that the prognostic impacts of BMI, total cholesterol, triglyceride and BP might be less powerful compared with those of LDL-C and diabetes. However, Nakatani et al reported that the metabolic syndrome, diagnosed from the combination of BMI, HDL-C, triglyceride, BP, and fasting blood glucose, was an independent predictor of subsequent combined cardiac events of cardiac death and non-fatal MI in Japanese patients after AMI. Therefore, it is plausible that the improvements in BMI, triglyceride and BP observed in the present study might contribute to the improvement in the long-term prognosis in Japanese AMI patients.

Future Direction
In the present study, the rate of active OPCR participation was only 24% (522/2191 patients) in the low prognostic risk group. To reduce lifetime CAD risk in these low prognostic risk AMI patients, a substantial increase in participation rate in OPCR is necessary. However, according to a recent nation-wide survey in 526 Japanese Circulation Society authorized cardiology training hospitals, the implementation rate was 92% for emergency PCI, but only 9% for OPCR. In addition, Ades et al reported that, by multivariate analysis, the strength of the physician’s recommendation for participation was the most powerful predictor of OPCR participation. Thus, to increase the participation rate in OPCR, it is critically important to greatly increase the number of CR facilities and to enhance physicians’ understanding of the benefits of OPCR after AMI.

Study Limitations
First, this study was a retrospective analysis and the number of patients was relatively small. The more active patients would be expected to participate in OPCR and this might have introduced a selection bias.

Second, the low prognostic risk group is anticipated to be at low risk in terms of short-term prognosis and hence, whether improvements in CRF profile in such low prognostic risk patients are associated with actual improvements in outcome is uncertain. A longer follow-up in a larger number of patients is necessary to increase the statistical power to demonstrate the beneficial effect of OPCR on the long-term prognosis.

Conclusions
The low prognostic risk AMI patients have a higher prevalence of multiple CRF than the non-low risk patients. Active participation in OPCR program is associated with improved exercise capacity and CRF profile in such low prognostic risk patients. OPCR program can be effective in achieving secondary prevention goals even in the low prognostic risk AMI patients.

Disclosure
Supported in part by Health and Labor Sciences Research Grant (H19-011) from the Ministry of Health, Labor and Welfare, Japan.

References


