Long-term Outcome in Single-vessel Coronary Artery Disease in Japanese Patients

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SUMMARY

We assessed the long-term outcome of medical therapy in 453 patients who underwent coronary angiography in the period from September 1973 to February 1984, and who had a significant stenotic lesion (75% or more stenosis) in a single coronary artery. The mean follow-up period was 9.8 years. The 5- and 10-year survival rates were, respectively, 96.0% and 91.3% in these patients, and these survival rates were comparable to the cumulative survival rates in the age-matched healthy male controls determined on the basis of overall death. Cardiac death occurred in 35/453 patients (7.7%) with single-vessel disease (SVD), and non-fatal myocardial infarction occurred in 17 patients (3.8%) during the follow-up period. The incidence of cardiac events, which was defined as cardiac death and nonfatal myocardial infarction, was as low as 1.2% per year. The survival rates were compared in terms of the presence or absence of myocardial infarction, the type of the coronary artery with stenosis, and proximal versus distal location of the stenotic lesion in the left anterior descending artery (LAD). The survival rates were similarly high in both assessed groups, with no significant differences. Patients with SVD treated medically had a good prognosis, except for those patients with decreased left ventricular function (ejection fraction ≤ 40%).

These factors should be taken into consideration when selecting therapies for patients with SVD. (Jpn Heart J 1996; 37: 165–175)

Key words: Coronary artery disease Single-vessel disease Medical treatment Long-term prognosis

LARGE-SCALE prospective randomized studies have shown that single-vessel coronary artery disease (SVD) can be successfully treated with either medical therapy or coronary artery bypass grafting (CABG) in Europe and the United States. Recently, however, percutaneous transluminal coronary
angioplasty (PTCA) has been used more often for the treatment of SVD than before, since PTCA has been shown to be superior to medical therapy in short-term improvement of symptoms and exercise tolerance. However, PTCA has not been compared with medical therapy with regard to the improvement of long-term survival.4) Assessment of the long-term outcome of medical therapy is also necessary for the evaluation of the long-term benefit of invasive treatment.

Therefore, we performed a retrospective study in patients with SVD, diagnosed by coronary angiography, at our institute in the period before the introduction of PTCA to assess the long-term outcome of medical therapy.

**Subjects and Methods**

**Subjects:** Among patients who underwent coronary angiography in the period from September 1973 to February 1984, when PTCA was introduced in our institute, 490 who had 75% or more organic stenosis in one of the major coronary arteries were enrolled in this study. Forty-five patients who underwent CABG within 1 year after coronary angiography were excluded. Patients who received reperfusion therapy, and patients with such complications as Kawasaki disease, valvular disease or cardiomyopathy were also excluded.

**Methods:** Coronary angiography was performed according to Sones' technique in all patients and left ventricular ejection fraction (EF) was calculated using Kennedy's formula.

Each patient's status was researched using a questionnaire sent by mail or by phone inquiry. When a patient's survival was confirmed, the current severity of angina, therapies used to date, the presence/absence and timing of such complications as acute myocardial infarction (AMI) and heart failure, if any, were investigated. When a patient's death was confirmed by a family member, the cause and date of death were recorded.

The date of coronary angiography was defined as the entry of follow-up, and final follow-up was performed on August 31, 1990.

**Definition of SVD:** American Heart Association (AHA) classification5) segment 8 of the left anterior descending artery (LAD), segments 12 and 14 of the left circumflex artery (LCX), the non-dominant right coronary artery (RCA), and segment 4 of the RCA were not included in the major coronary arteries. The first diagonal branch (segment 9) of a similar size to that of the LAD and segment 12 having a large perfusion area were included in major coronary arteries. The cases in which 75% or more stenosis was present in both segments 12 and 14, and in both the posterior descending branch and the atrioventricular branch of segment 4 (4PD and 4AV, respectively), were included in SVD.

**Definition of nonfatal cardiac events:** Surviving cases of congestive heart failure
Table I. Subjects According to the Presence or Absence of Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>AP</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>276</td>
<td>177</td>
<td>453</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.1 ± 9.7</td>
<td>55.2 ± 8.9</td>
<td>53.3 ± 9.5</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
<td>115.6 ± 38.8</td>
<td>120.8 ± 39.3</td>
<td>117.6 ± 39.3</td>
</tr>
<tr>
<td>Vessels involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>174</td>
<td>122</td>
<td>296</td>
</tr>
<tr>
<td>RCA</td>
<td>64</td>
<td>23</td>
<td>87</td>
</tr>
<tr>
<td>LCX</td>
<td>25</td>
<td>31</td>
<td>56</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; AP = angina pectoris; LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery.

(CHF) and AMI, which occurred during the study period, as well as invasive treatment, such as PTCA and CABG, were defined as nonfatal cardiac events. AMI followed by death within 1 month was defined as cardiac death and was not included in nonfatal cardiac events.

Statistical analysis: A cumulative survival curve was generated based on cardiac death, using the Kaplan-Meier method. Noncardiac deaths and cases undergoing PTCA or CABG during medical therapy were handled as dropouts. Statistical significance of differences in the survival curve was tested using the generalized Wilcoxon test. Frequencies were compared using the chi-squared test, and a p value < 0.05 was taken as the level of statistical significance.

Follow-up rate and composition of the patients followed-up: Follow-up was possible in 453 of 490 patients (92.1% follow-up rate), 426 males and 27 females (mean age was 53.3 ± 9.5 years). The mean follow-up period was 117.6 ± 39.3 months (9.8 years). The composition of the 453 patients is shown in Table I.

There were 276 patients with a history of myocardial infarction (60.9%; MI group) and 177 patients without a history of myocardial infarction (39.1%; angina pectoris (AP) group).

RESULTS

Clinical outcome (Table II): Nonfatal cardiac events occurred in 73/453 patients (16.1%), although AMI was infrequent, occurring in 17/453 patients (3.8%), and invasive treatment, CABG or PTCA, accounted for the majority of nonfatal cardiac events (41 and 21 patients, respectively). Cardiac death occurred in 35 patients (7.7%) during the follow-up period, and non-cardiac death occurred at the same frequency.

In a comparison between the MI and AP groups, cardiac death was more frequent in the MI group than in the AP group and nonfatal cardiac events such
Table II. Incidence of Death and Nonfatal Cardiac Events

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Death</th>
<th>Nonfatal cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac</td>
<td>Noncardiac</td>
</tr>
<tr>
<td>SVD</td>
<td>453</td>
<td>35</td>
</tr>
<tr>
<td>MI</td>
<td>276</td>
<td>23</td>
</tr>
<tr>
<td>AP</td>
<td>177</td>
<td>12</td>
</tr>
</tbody>
</table>

*Total number of nonfatal cardiac events indicate number of patients. AMI = acute myocardial infarction; CHF = congestive heart failure; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass graft surgery; AP = angina pectoris.

as AMI were more frequent in the AP group.

Considering cardiac death and nonfatal myocardial infarction together as cardiac events, the incidence of so-defined cardiac events in the 9.8-year follow-up period was as low as 11.5% in all patients with SVD, 13.0% in the MI group, and 10.5% in the AP group.

Among the patients who had an episode of AMI during the follow-up period, AMI occurred in the same coronary artery that had a stenotic lesion in the initial coronary angiography in only 4 patients in the AP group, and in 1 in the MI group. The lesion responsible for AMI developed in other vessels in the other 10 patients, excluding 2 patients in whom the location of the responsible lesion could not be identified.

**Changes in clinical symptoms in patients without MI (Figure 1):** It was possible to compare the severity of the symptoms of angina pectoris at the final follow-up with that at the time of enrollment in 116 patients in the AP group, excluding those who died or had a cardiac event during the follow-up period. Symptoms improved as a result of medical therapy in 103/116 patients (88.8%). The NYHA classification was grade 3 or higher in 41 patients at the time of enrollment, and in only 1 at the time of follow-up after a mean of 10 years. The NYHA classification was grade 1, indicating asymptomatic conditions, in 95/116 patients at the time of follow-up.

**Causes of cardiac death:** Cardiac death was ascribable to myocardial infarction in 19 patients, sudden death in 15, and heart failure in 1. In the MI group, sudden death accounted for cardiac death in more than half of the cases (12/23 patients), and in the AP group, myocardial infarction was the predominant cause of cardiac death (8/12 patients).

**Cumulative survival curve (Figure 2):** The 5-year survival rate was 96.0% and the 10-year survival rate 91.3% in all patients with SVD, indicating a good prognosis in patients undergoing medical therapy. These survival rates were comparable to the survival rates for the age-matched healthy male control group generated by the Kaplan-Meier method based on all deaths. In the MI group,
Figure 1. Changes in angina pectoris status in patients without myocardial infarction.

Figure 2. Cumulative survival curves for patients with SVD and normal controls. Survival curve for normal controls was generalized based on all deaths.

the 5- and 10-year survival rates were, respectively, 95.5% and 90.9%, and in the AP group 96.5% and 91.8%, indicating that the prognosis of medically treated single-vessel coronary artery disease (SVD) is not affected by history of myocardial infarction.
Cumulative event-free curve (Figure 3): When cardiac events were defined as episodes of AMI or CHF and treatment with PTCA or CABG, the 5- and 10-year cardiac event-free survival rates were 90.4% and 77.4% in all patients with SVD. Comparing groups with and without a history of myocardial infarction, the 5- and 10-year cardiac event-free survival rates were 91.9% and 78.3% in the MI group, and 88.1% and 75.6% in the AP group, showing no difference between the two groups.

Survival curve classified by diseased coronary artery (Figure 4): The 5- and 10-year cumulative survival rates were classified by the diseased coronary artery. The 5- and 10-year survival rates were 95.1% and 90.8% in patients with LAD stenosis, 97.6% and 90.7% in patients with RCA stenosis, and 96.3% and 96.3% in patients with LCX stenosis. Although the long-term survival rate was slightly higher in patients with LCX stenosis, there was no significant difference in prognosis according to the diseased coronary artery.

The survival rates by diseased coronary artery were compared between groups with and without a history of myocardial infarction. In the MI group, the 5- and 10-year survival rates were 94.1% and 89.8% in patients with LAD stenosis, 96.7% and 88.5% in patients with RCA stenosis, and 100% and 100% in patients with LCX stenosis. In the AP group, the corresponding survival rates were 96.6% and 92.3% in patients with LAD stenosis, 100% and 95.0% in patients with RCA stenosis, and 93.2% and 86.0% in patients with LCX stenosis.

The 5- and 10-year cumulative cardiac event-free survival rates were 90.5% and 79.1% in patients with LAD stenosis, 89.7% and 74.3% in patients with RCA stenosis, and 89.2% and 69.3% in patients with LCX stenosis, showing no
significant differences in the event-free survival rates according to the diseased coronary artery.

**Survival in patients with proximal LAD lesions (segment 6 stenosis) in the AP group (Figure 5):** When a stenotic lesion at a site proximal to the first septal perforator of the LAD was defined as a proximal LAD lesion (segment 6), the 5- and 10-year survival rates for patients with a proximal lesion were 95.0% and 90.7%. Although these survival rates were slightly lower than those for patients with a lesion in a distal site (98.2% and 93.7%), no significant differences were found between the two groups.

There was no significant difference between proximal LAD and distal LAD lesion groups with regard to the cumulative cardiac event-free survival rate.

**Left ventricular ejection fraction (EF) and survival (Figure 6):** The relation-
Figure 6. Cumulative survival curves for patients with myocardial infarction according to the ejection fraction.

ship between EF and cumulative survival rate was assessed in the MI group. The patients were divided into 3 groups, having EF of 60% or above, 41%–59%, and 40% or below, for comparison of survival rate. The 5- and 10-year survival rates were 96.7% and 94.5% in patients with EF of 60% or above and 97.9% and 89.9% in patients with EF of 41%–59%, indicating a good prognosis. In patients with decreased left ventricular function (EF below 40%), the 1-year survival rate was as low at 87.5%, and the 5- and 10-year cumulative survival rates decreased to 79.2% and 74.8%.6)

**DISCUSSION**

We have previously reported that medically treated Japanese patients with coronary artery disease have a better prognosis than patients in Western countries.6,7) In the present study, we assessed the outcome of medically treated patients with single-vessel coronary artery disease.

**Survival rate:** The previous studies have shown that patients with SVD have a good prognosis in the United States and Europe,1-3,8) while there have been few studies on the prognosis of such patients in Japan.6,7,9-11) Hosoda conducted the first multicenter study, and reported that the 5-year survival rate in patients with SVD was 95%, with no significant differences among groups based on the type of diseased coronary artery.9) The present study documented survival rates consistent with the previous data, and it also showed that the cardiac death-based survival rate for patients medically treated for SVD was as good as the survival
rate in age-matched healthy male controls based on non-specific death. We also found that there was no difference in the survival rates between SVD patients with and without myocardial infarction.

It has also been reported that patients with LAD stenosis have a poorer prognosis than cases of SVD in other coronary arteries\textsuperscript{7,12-13} and that a proximal LAD lesion is related to a poorer prognosis than distal LAD lesions.\textsuperscript{7,14} However, discrepant findings also have been reported, and no conclusive arguments have yet been advanced for the difference in the prognosis of coronary artery disease in relation to the type of diseased coronary artery.\textsuperscript{1,3,15} In the present study, survival rate was assessed in patients with and without a history of myocardial infarction, and no significant differences were found in the survival rates in relation to the type of diseased coronary artery or proximal/distal site of the location of lesions in the LAD. However, we do not think that this result negates the significance of the LAD in multivessel coronary disease.

**Incidence of cardiac events:** In the present study, the incidence of cardiac events, defined as cardiac death and nonfatal myocardial infarction, was as low as 11.5\% in the 9.8-year follow-up period, or 1.2\% per year. The 5-year incidence of cardiac events (cardiac death and myocardial infarction) in patients with SVD has been reported to be 15–20\% in the United States and Europe\textsuperscript{8,16} and the cumulative probability of remaining free of cardiac events reported recently was 69\% at 10 years.\textsuperscript{3} In the present study, the incidence of nonfatal cardiac events may have been somewhat underestimated because it was investigated using a questionnaire. Even when such a possibility is taken into account, the incidence of nonfatal myocardial infarction was far lower than that reported in Western countries, as was the case for survival rate, indicating a better prognosis of coronary artery disease in Japanese patients. Furthermore, as pointed out previously and confirmed in the present study, symptoms improved as a result of medical therapy in the majority of patients with SVD, although it takes a longer time for medical therapies to ameliorate symptoms than it does for surgical treatment.\textsuperscript{4,8} Therefore, these features of SVD in Japanese patients should be taken into account in determining a therapeutic regimen for SVD in Japanese patients.

In patients who had an episode of AMI during the follow-up, AMI commonly developed in a vessel other than that involved in the MI detected in the initial coronary angiography. This result was consistent with the previous finding that the lesions of coronary atherosclerosis do not extend linearly but extend in a jumping-up manner, and therefore it is difficult to predict the progression of coronary atherosclerosis by repeating coronary angiography.\textsuperscript{17,18}

**Left ventricular ejection fraction (EF):** Although the prognosis of SVD was generally good, the survival rate in patients with EF of below 40\% was lower (87.5\%), even in the first year. This result agreed with the previous reports point-
ing out that EF is a more significant prognostic factor of coronary artery disease than the number of diseased coronary arteries.3,19)

Although patients undergoing reperfusion therapy were not included in the present study, the results suggest that reducing infarction size by reperfusion therapy is important in the exacerbation phase of acute myocardial infarction from the perspective of long-term prognosis. Cardiac death, probably due to tachyarrhythmia, accounted for the majority of cardiac deaths in patients with decreased left ventricular function. Therefore, strict control of arrhythmia was suggested to be necessary in patients with decreased left ventricular function.

**Conclusions**

There have been a few reports on the outcome of medical therapy in patients with coronary artery disease, and selection of therapies for coronary artery disease is routinely based on data obtained in the United States or Europe, despite the observation that the incidence of cardiac events in those populations is relatively high and the survival rate is lower than in Japanese. While the evaluation of PTCA has not yet been established in comparison with other therapies, PTCA is commonly indicated for the treatment of coronary artery disease, including SVD. However, PTCA is often followed by complications at the acute stage, such as acute coronary occlusion, as well as coronary restenosis, which remains to be challenged.

We therefore retrospectively investigated the long-term outcome of medically treated Japanese patients with single-vessel coronary artery disease, and found that medical treatment can produce an excellent long-term prognosis in Japanese patients with SVD, with a low incidence of cardiac events. Symptoms of angina pectoris were also improved by medical treatment, although improvement of symptoms was achieved after a longer time with medical treatment than with surgical treatment. These findings should be taken into consideration in selecting therapies for single-vessel coronary disease.

**References**

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