Clinical Studies

Long-term Prognosis in 990 Medically Treated Japanese Patients with Coronary Artery Disease

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SUMMARY
We performed a retrospective analysis of the fate of 990 medically treated Japanese patients with coronary artery disease. Patients were enrolled in this study between September 1973 and February 1984. They were confirmed to have significant coronary artery disease by coronary angiography. There were 924 males and 66 females with a mean age of 54.4 years. The mean duration of follow-up was 9.4 years with a range of 6.5 to 17.0 years. The 5-year and 10-year survival rates for the entire population were 92.1% and 84.4%. The 5-year and 10-year survival rates in patients with single- (SVD), double- (DVD), and triple-vessel disease (TVD) and left main trunk (LMT) disease were as follows: 96.0% and 91.9% for SVD, 93.8% and 87.5% for DVD, 83.2% and 68.3% for TVD, and 89.3% and 84.6% for LMT disease.
This was the first large follow-up study of coronary artery disease in Japan. Its results suggest that the prognosis of Japanese patients with coronary artery disease is more favorable than that of patients in Western countries. In addition, the findings should provide a control data base for future studies in Japan and the West. (Jpn Heart J 34: 539–550, 1993)

Key words: Survival rate Medical treatment Number of diseased coronary arteries Left ventricular ejection fraction Nonfatal cardiac event

INTERVENTIONAL therapy, such as percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG), has come to be a major method for treating coronary artery disease. The short-term effectiveness of such treatment in achieving the improvement of symptoms has been well established. However, PTCA is frequently associated with acute complications, and restenosis remains a major problem over the longer term. It has recently been shown that the long-term efficacy of CABG is not always superior to that of medical treatment because vein grafts often became occluded with the passage of time...
In addition, the ultimate aim of treating coronary artery disease is not merely symptomatic relief, but the prevention of cardiac events and improvement of the long-term prognosis. Furthermore, data on the long-term prognosis of PTCA are not yet sufficient to allow conclusions to be drawn. Thus, medical treatment which can reduce coronary risk factors remains important.

To assess the long-term efficacy of interventional therapy in patients with coronary artery disease, it is necessary to clarify the long-term outcome of medical treatment and compare the results with those of interventional therapy. In Japan, there have been only a few studies performed on the long-term prognosis of medically treated patients with coronary artery disease, and there has been no large-scale study of patients treated at a single institution. In this era of increasingly aggressive interventional treatment, it may soon become impossible to evaluate the long-term efficacy of the medical treatment of coronary artery disease.

Accordingly, we investigated the long-term prognosis of patients with coronary artery disease who were managed medically at our hospital before the introduction of PTCA. Coronary angiography was performed in all subjects and the mean follow-up period was 9.4 years.

Subjects and Methods

Subjects

Out of 3,100 consecutive patients who underwent coronary angiography between September 1973 and February 1984 when PTCA was introduced to our hospital, 990 patients diagnosed as having significant coronary artery disease and receiving medical therapy for at least 1 year were selected as the subjects of this study. Significant disease was defined as 75% or greater luminal narrowing of at least one major coronary artery, except for >50% narrowing for the left main trunk. Patients with lesions in the major coronary vessels due to aortitis or Kawasaki disease were excluded, and patients having valvular disease or cardiomyopathy were also excluded.

Methods

Coronary angiography was performed using the Sones technique with a Cardiodiagnost apparatus (Philips) and 35 mm cine film. Images were taken from multiple directions before and after sublingual NTG administration to obtain good visualization of the lesions and to assess the severity of stenosis. Patients were classified as having single- (SVD), double- (DVD), or triple-vessel disease (TVD). Patients having a lesion in the left main coronary trunk were categorized
as having left main trunk (LMT) disease irrespective of the number of other diseased vessels. Left ventriculography was generally performed in the 30-degree right antero-oblique and 60-degree left antero-oblique positions and the left ventricular ejection fraction (EF) was calculated using the method of Kennedy.

**Data acquisition**

A questionnaire was used for investigation of the prognosis. The questionnaire was either mailed to patients or they were questioned directly by telephone. After having confirmed that the patient was alive, inquiries were made concerning the present severity of angina pectoris, the details of the treatment performed to date, the presence of complications such as myocardial infarction and heart failure, and the date of the occurrence of any such complications. If the patient had died, the cause and date of death were determined. The development of heart failure or acute myocardial infarction (MI) as well as interventions such as PTCA or CABG were defined as nonfatal cardiac events. Episodes of acute MI which led to death within 1 month were separated from nonfatal cardiac events and were regarded as cardiac death.

The date of entry was defined as the day when the patient underwent coronary angiography, and follow-up for this study was completed on August 31, 1990.

**Statistical analysis**

A cumulative survival curve for cardiac death was generated according to the Kaplan-Meier method. Thus, death from noncardiac causes and patients who received CABG during the course of medical treatment were considered as being dropouts after the occurrence of such an episode. When a patient underwent PTCA, this was not counted as dropping out and was considered to be continuing medical treatment. The significance of between-group differences in survival was assessed using the generalized Wilcoxon test. The chi-squared test was used for the comparison of categorical variables and a difference of \( p < 0.05 \) is considered significant.

**RESULTS**

**Completeness and duration**

Follow-up was possible in 899/990 patients for a follow-up rate of 90.1%. The subjects were 833 males and 66 females with a mean age of 54.8 years and a mean follow-up period of 113.8 months (9.4 years).

The composition of the 899 patients in terms of the number of diseased coronary arteries is shown in Table I. There were 453 patients with SVD
(50.4%), 220 with DVD (24.5%), 198 with TVD (22.0%), and 28 with LMT (3.1%). There were 552 patients with a history of MI (61.4%) and 347 without any such history (38.6%).

Clinical outcome in relation to the number of diseased coronary arteries (Table II)

Of the 453 patients with SVD, 73 (16.1%) had nonfatal cardiac events. The incidence of acute MI was low in this group, occurring in only 17 patients (3.8%). The various types of interventional therapy accounted for most of the nonfatal cardiac events, including CABG in 41 patients and PTCA in 21. There were 35 cardiac deaths (7.7%) and another 35 deaths from noncardiac causes (7.7%).

In the DVD group, 59 patients (26.8%) had nonfatal cardiac events, including acute MI in 16 (7.3%) and CABG in 40 (18.2%). There were 31 cardiac deaths (14.1%) in this group, an incidence almost double that in the SVD group.

In the TVD group, 60 patients (30.3%) had nonfatal cardiac events including acute MI in 6 cases (3%). The overall incidence of nonfatal cardiac events in
this group was comparable to that in the DVD group, although the incidence of acute MI was lower than in the DVD group. Forty-seven TVD patients (23.7%) underwent CABG, and their prognosis was favorable. On the other hand, the patients who continued to be treated medically had a poor prognosis, as indicated by the occurrence of cardiac death in 73 cases (36.9%).

Of the 28 patients with LMT, 12 (42.9%) also received CABG and 16 patients continued to be treated medically. Cardiac death occurred in only 4 patients in this group (14.3%) and the incidence was similar to that in the DVD group.

In the total population of 899 patients, the incidences of acute MI and heart failure were 4.6% and 1.6%, respectively. Nonfatal cardiac events including PTCA and CABG occurred in 22.6% of this population and cardiac death in 15.9%.

**Incidence of cardiac death and nonfatal MI (Table III)**

Considering cardiac death and nonfatal MI together as ischemic events, the incidence was 11.5% in the SVD group, 18.6% in the DVD group, 39.9% in the TVD group, and 17.9% in the LMT group. The overall incidence was 20.4% in the 899 patients.

**Causes of cardiac death (Table IV)**

Cardiac deaths in the SVD group included 18 sudden deaths, 16 deaths from MI, and 1 death from heart failure. The percentage of sudden death increased in the DVD and TVD groups to 61% and 76%, respectively.

**Cumulative survival according to the number of diseased coronary arteries (Fig. 1)**

The cumulative survival curves for patients in the SVD, DVD, TVD, and LMT groups who were medically treated are shown in Figure 1.

| Table III. Cardiac Events (Cardiac Death and/or Nonfatal MI) |
| --- | --- | --- |
| Number of patients | Cardiac events | Total (%) |
| | | Cardiac death | MI |
| SVD | 453 | 35 | 17 | 52 (11.5) |
| DVD | 220 | 31 | 16 | 47 (21.4) |
| TVD | 198 | 73 | 6 | 79 (39.9) |
| LMT | 28 | 4 | 1 | 5 (17.9) |
| Total | 899 | 143 | 40 | 183 (20.4) |

SVD=single vessel disease; DVD=double vessel disease; TVD=triple vessel disease; LMT=left main trunk; MI=myocardial infarction.
Table IV. Cause of Cardiac Death

<table>
<thead>
<tr>
<th></th>
<th>MI</th>
<th>Sudden death</th>
<th>CHF</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
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<td>18</td>
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<td>0</td>
<td>35</td>
</tr>
<tr>
<td>DVD</td>
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<td>31</td>
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<tr>
<td>TVD</td>
<td>15</td>
<td>45</td>
<td>13</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>LMT</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>86</td>
<td>19</td>
<td>1</td>
<td>143</td>
</tr>
</tbody>
</table>

SVD=single vessel disease; DVD=double vessel disease; TVD=triple vessel disease; LMT=left main trunk; MI=myocardial infarction; CHF=congestive heart failure.

Fig. 1. Cumulative survival curves according to the number of diseased coronary arteries. Differences in survival were significant between TVD and, both SVD and DVD (p<0.05).

The 5-year survival rate of patients with SVD was 96% and the 10-year rate was 91.9%, so the prognosis was clearly quite favorable for SVD patients. The survival rate of patients with DVD resembled that of SVD patients, being 94.5% at 5 years and 87.4% at 10 years. The prognosis was relatively favorable in patients with DVD. In contrast, the survival rate of patients with TVD was 80.7% at 5 years and 64.2% at 10 years, showing a significant difference from the patients with SVD and DVD. Thus, the long-term prognosis of TVD patients was particularly unfavorable. The survival rate of patients with LMT was 89.3% at 5 years and 84.6% at 10 years, which was similar to the DVD patients. The survival rate of the overall population with medically treated coronary artery
Correlation with left ventricular ejection fraction (EF) (Fig. 2)

The relationship between mortality and left ventricular EF was assessed in all patients with a history of MI (MI group). The patients were classified into 3 groups (EF≥60%, EF 41–59%, and EF≤40%). As the EF decreased, the mortality rate increased in either TVD, DVD, or SVD. In patients with an EF≥60%, the mortality was 5.1% in SVD, 13.7% in DVD, and 23.1% in TVD, contrasting with rates of 25% in SVD, 33.3% in DVD, and 64.3% in TVD for patients with an EF≤40%. Thus, the mortality rate exceeded 50% in patients with an EF≤40% and TVD.

Discussion

Coronary artery disease is less common in Japan than in Western countries, and it has generally been thought that Japanese patients have a relatively favorable prognosis. However, there have been only a few investigations of the long-term prognosis of coronary artery disease in Japan and no large-scale studies including coronary angiography which compared the prognosis to the extent of coronary artery pathology have been performed.

Saito et al reported a 12% 5-year cardiac death rate in hospital survivors of myocardial infarction, but they performed coronary angiography in only about half of the patients and their population was confined to those patients with myocardial infarction. Although the present study was performed retrospectively it is the first attempt to assess the long-term prognosis of a large population of
medically treated patients with angiographically confirmed significant coronary artery disease in Japan.

**Survival**

The survival rate of patients with coronary artery disease has improved over time.\(^{13}\) In 1973, Bruschke reported that the 5-year survival rate was 65.7% in his series of cardiac patients undergoing medical treatment.\(^{14}\) A Veterans' Administration study published in 1984 showed that the 5- and 11-year survival rates were 78% and 57%, respectively.\(^{3}\) In the 12-year European Coronary Surgery Study (ECSS) that was published in 1988, the 5-year survival rate was 83.1% while the 10-year survival rate was 66.7%.\(^{15}\) In the Coronary Artery Surgery Study (CASS) which was published in 1990, the 5- and 10-year survival rates of 390 medically treated patients were 92% and 79%, respectively, thus showing improvement.\(^{16}\)

A comparison of these results with those of the present study reveals that both 5-year and 10-year survival rates were better in the present study. There are several limitations to a direct comparison with other reports, however, because of differences in the study populations. One difference between CASS and the present study is that severe cases of LMT, patients with EF<35%, and patients aged over 65 years were excluded from CASS, so that coronary artery disease might have been less severe in that study than in the present study. Taking this into consideration, it appears that Japanese patients with coronary artery disease have a favorable prognosis in terms of 10-year survival.

*The number of diseased coronary arteries and survival rate*

The number of diseased coronary arteries and the left ventricular ejection fraction are considered to be important predictors of prognosis in coronary artery disease.\(^{17}-^{19}\) Proudfit et al reported in 1978 that the 5-year survival rate was 85% in SVD, 62% in DVD, 47% in TVD and 51% for LMT disease.\(^{20}\) The CASS showed that the 5-year survival rates for SVD, DVD, TVD, and LMT were 93%, 93%, 90%, and 83%, respectively, and the 10-year rates were 82%, 79%, 75%, and 50%.\(^{16}\) Our results are generally in accordance with those of the CASS data. However, the survival rate of TVD patients was lower in the present study at both 5 and 10 years. This is considered to be because patients with poor left ventricular function, as indicated by an EF <35%, were excluded from the CASS, while the present study included 28 patients with TVD who had an EF ≤40%, and also because 53% of the patients with TVD received surgical treatment during the follow-up period in the CASS while only 24.7% did so in our study.

A previous study conducted in Japan by Hosoda et al showed the 5-year
survival rates for SVD, DVD, TVD and LMT were 95%, 84%, 62%, and 78%, respectively. The 5-year survival rates in our study were higher than these data. The reason for this difference is not clear, but our data agree with other data from studies in Japan. The study by Hosoda et al was the first multicenter trial in Japan and only 2% of the patients in his series underwent CABG during medical treatment. This may explain the lower survival rate reported in his study.

In the present study, the survival of patients with LMT disease was better than that reported in other studies. The reason for this is uncertain, but it may be because patients with LMT lesions were carefully managed and subjected to surgical treatment whenever necessary. As a consequence, only patients with relatively mild disease (a single LMT lesion with 50% stenosis) remained on medical treatment.

Left ventricular ejection fraction (EF) and survival

It has previously been shown that the left ventricular EF is the most significant determinant of the prognosis of ischemic heart disease. Harris et al reported that the 5-year survival rate was 89% in patients with normal left ventricular function, 70% in patients with moderately impaired left ventricular function, and 38% in patients with severely impaired left ventricular function. In the CASS, the 10-year survival rate was 84% for patients with relatively intact left ventricular function and it was 61% for patients with an EF <50%. In this study, patients with a history of MI were divided into 3 groups on the basis of EF to assess the relationship between EF and survival. Regardless of the number of diseased coronary arteries, the survival rate in patients with a low EF was worse than that in patients with a normal EF. This result supported previous findings suggesting that EF is a more important determinant of the prognosis of coronary artery disease than the number of vessels involved.

Nonfatal cardiac events

In addition to MI and heart failure, PTCA or CABG were also treated as nonfatal cardiac events in this study. Nonfatal cardiac events were observed in 22.6% of all patients, including MI in 4.6%, heart failure in 1.6%, PTCA in 3.3%, and CABG in 15.6%. Therefore, the incidence of nonfatal cardiac events was very low except for CABG.

In the multi-center study conducted by Hosoda et al, nonfatal MI occurred in 4.1% of patients in the mean follow-up period of 5 years. Harris et al reported that the cumulative rate of nonfatal MI was 18% at 7 years. In the CASS, the cumulative probability of remaining free of cardiac death and nonfatal MI was 69% at 10 years. Therefore, taken together with the survival rate, the low incidence of nonfatal MI also suggests that the long-term prognosis of
coronary artery disease is better in Japanese patients.

It was also observed that the incidence of nonfatal MI was low in TVD patients despite their high incidence of cardiac death; this finding agreed with the CASS data.\(^{16}\) It may be that the development of acute MI directly causes cardiac death in patients with TVD, as opposed to those with SVD or DVD.

**Limitations of this study and subjects for future investigation**

The present study is not a randomized controlled trial but a retrospective review, so there may be some bias in the selection of subjects. We suspect that the lower percentage of women in this study compared with the other study is due to a bias in the selection process. That is, coronary arteriography was performed less aggressively in women than in men due to their more advanced age and lower level of social activity. However, all the patients included in this study were initially seen before the introduction of PTCA at our hospital, and most of them were enrolled even before the establishment of a department of cardiovascular surgery at our hospital. Therefore, the subjects of this study exhibited marked variations in the severity of disease. Some were asymptomatic after suffering MI, some should have undergone surgical treatment, and some were too unfit for surgery. In addition, since a large number of patients (990) were enrolled, the distribution of disease in this study is considered to be representative of coronary artery disease in Japan.

During the long-term medical management of patients with coronary artery disease, interventional treatment such as PTCA or CABG should be employed if angina pectoris appears to be resistant to drug therapy. Along with various technical advances and improvements in these interventional procedures, more and more patients are undergoing interventional therapy while on medical treatment, and this should contribute to improving the prognosis. This is thought to be partly responsible for the improvement in the prognosis of ischemic heart disease in the USA and Europe,\(^{13}\) in addition to the utilization of \(\beta\)-blocking agents and Ca antagonists.

In Japan, it is common for PTCA to be chosen as the initial treatment for coronary artery disease, although the long-term usefulness of PTCA has not yet been well established. It is thus also necessary to investigate the long-term efficacy of PTCA in patients undergoing this treatment, including unsuccessful cases, and to compare the results with the data for CABG and medical treatment. Additionally, we think it is necessary to investigate the relationship between the prognosis in coronary artery disease and the changes in the coronary risk factors such as serum cholesterol, diabetes mellitus, and hypertension.

In conclusion, this study showed that medically treated Japanese patients with coronary artery disease have a better prognosis than patients in Western
countries.

REFERENCES


