Long-term Outcome in Triple-vessel Coronary Artery Disease in Medically Treated Japanese Patients

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SUMMARY

The long-term outcome in 198 patients with triple-vessel disease (TVD) treated medically was investigated. The patients, who underwent coronary angiography between September 1973 and February 1984, had significant (75% or more) stenotic lesions in all three major coronary arteries. The mean follow-up period was 8.4 years. The 5- and 10-year survival rates were 80.7% and 64.2%, respectively. Cardiac death occurred in 73 patients (36.9%) and nonfatal cardiac events developed in 60 patients (30.9%) during follow-up. When cardiac death and nonfatal myocardial infarction (MI) were defined as cardiac events, the annual attrition rate was 4.7%. There was no difference in survival with regard to the presence or absence of MI, the site of infarction, or the presence of total occlusion. In the AP group, however, the survival rate decreased as the number of totally-occluded arteries increased. In the MI group, the survival rate was not altered by the number of totally-occluded arteries, but was affected by the ejection fraction (EF). The 5-year survival rate was better in patients with good left ventricular function ($EF \geq 60\%$) than in those with impaired left ventricular function ($EF < 60\%$), although the 10-year survival rate was similarly low in both groups. Revascularization such as PTCA or CABG might improve the long-term outcome in patients with TVD. (*Jpn Heart J* 1998; 39: 67-77)

Key words: Coronary artery disease, Triple-vessel disease, Medical treatment, Ejection fraction, Long-term prognosis, Total occlusion

IN the United States and Europe, the prognosis of coronary artery disease has been extensively studied, and it has been reported that the outcome of medical treatment for patients with triple-vessel disease (TVD) is inferior to that of coronary artery bypass grafting (CABG).¹⁻³⁾

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In Japan, however, the prognosis of TVD has been assessed in only a few small studies, and no studies that classified subjects by the number of involved arteries on coronary angiography have been performed.⁴⁻⁷⁾ Therefore, we performed a retrospective study on the long-term outcome of medical treatment for patients with TVD diagnosed by coronary angiography at our hospital, and analyzed the prognosis of TVD in relation to myocardial infarction, left ventricular function, and the presence of total coronary artery occlusion to find important prognostic factors.

SUBJECTS AND METHODS

Subjects: Among patients who were diagnosed as having 75% or greater organic stenosis of all three major coronary arteries by coronary angiography at our institution from September 1973 to February 1984 before the introduction of percutaneous transluminal coronary angioplasty (PTCA), we enrolled 227 patients in this study after excluding 75 patients who underwent CABG within one year of diagnosis. Patients who received reperfusion therapy and those with Kawasaki disease, valvular heart disease, or cardiomyopathy were also excluded.

Methods: Coronary angiography was performed using the Sones technique and the left ventricular ejection fraction (EF) was determined using Kennedy's formula. Stenosis of the coronary arteries was assessed visually.

The prognosis was investigated using a questionnaire sent by mail or by telephone interview. After determination of survival or death, the following data were collected for surviving subjects: the current severity of angina, the therapeutic history and the presence/absence, as well as the time of onset of such complications as acute myocardial infarction (AMI) and heart failure. For deceased subjects, the causes and date of death were obtained from the family. The date of coronary angiography was defined as the entry of follow-up, and the final follow-up was performed on August 31, 1990.

Definition of major coronary arteries: The major coronary arteries were defined as segments 1, 2, 3, 6, 7, 11, and 13 in the American Heart Association (AHA) classification.⁸⁾ If the circumflex arteries (segments 12 and 14) were clearly larger than segments 11 and 13, they were included in the assessment. Patients complicated with left main trunk disease were handled independently and were excluded from this study.

Definition of nonfatal cardiac events: Nonfatal cardiac events were defined as congestive heart failure (CHF) and AMI that developed during the course of follow-up, as well as invasive treatment such as PTCA or CABG. AMI followed by death within one month was regarded as cardiac death instead of a nonfatal cardiac event.

Table I. Subjects According to the Presence or Absence of Myocardial Infarction

	MI	AP	Total
Number of patients	137	61	198
female	10	10	20
age(years)	56.4 ± 8.4	56.2 ± 9.3	56.3 ± 8.7
Follow-up period (months)	98.7 ± 50.8	105.5 ± 52.7	100.8 ± 51.5
Presence of Totally-occluded vessel	97	31	128
one vessel	67	24	91
two vessels	25	7	32
three vessels	5	0	5
Location of MI			
anterior	62		62
inferior	73		73
posterior	5		5

MI = myocardial infarction; AP = angina pectoris.

Definition of chronic total occlusion (CTO): Chronic total occlusion (CTO) of the coronary artery was defined in accordance with the criteria of the Thrombolysis in Myocardial Infarction (TIMI) study.⁹⁾ Coronary arteries having no or minimal antegrade perfusion (TIMI grade 0 or 1) were defined as chronic totally-occluded irrespective of the relation to myocardial infarction (MI).

Statistical analysis: A cumulative survival curve was generated based on cardiac death using the Kaplan-Meier method. Noncardiac deaths and patients who underwent PTCA or CABG during medical therapy were handled as dropouts after such an event. Differences in survival between the 2 groups were tested for statistical significance using the generalized Wilcoxon test. For comparison of survival between multiple groups, the log-rank test was performed. The chi-squared test was used for comparison of categorized variables. A *p* value less than 0.05 was taken to indicate a significant difference.

Follow-up rate and composition of the patients followed up: Follow-up was possible in 198 of 227 patients, with the follow-up rate being 87.2%. They comprised 178 males and 20 females with a mean age of 56.3 ± 8.7 years. The mean follow-up period was 100.8 ± 51.5 months (8.4 years). A clinical profile of the 198 patients is shown in Table I. 137 patients had a history of MI (60.9%; MI group) and 61 patients did not (39.1%; AP group). Four patients with inferior MI had also suffered from anterior MI. CTO was present in 97 patients in the MI group (affecting one vessel in 67 patients, 2 vessels in 25 patients, and 3 vessels in 5 patients) and 31 patients in the AP group (affecting one vessel in 24 patients and 2 vessels in 7 patients).

RESULTS

Clinical outcome (Table II): Of the 198 patients, 60 (30.3%) had nonfatal cardiac events, although the predominant event was CABG (23.7%) and the incidence of CHF or AMI was low, 4.5% and 3.0%, respectively. Cardiac death occurred in 73 patients (36.9%), and was 3 times more frequent than noncardiac death, which occurred in 23 patients. When the MI and AP groups were compared, the incidence of cardiac death was higher in the MI group, although not significantly. However, the incidence of nonfatal cardiac events such as AMI was higher in the AP group ($p = 0.04$). Considering cardiac death and nonfatal MI together as cardiac events, the incidence of such events was high, being 39.9% (4.7%/year) in all patients with TVD, 40.1% (4.9%/year) in the MI group, and 39.3% (4.5%/year) in the AP group.

Causes of cardiac death: The cardiac death was ascribable to sudden death in 45 patients, MI in 15, and heart failure in 13. In the MI group, sudden death was predominant among the cases of cardiac death (12/23). In the AP group, how-

Table II. Incidence of Death and Nonfatal Cardiac Events

Number of patients	Death			Nonfatal cardiac events				
	Cardiac	Noncardiac	Total	AMI	CHF	PTCA	CABG	Total*
TVD	73	23	96	6	9	2	47	60
MI	53	18	71	2	7	0	30	35
AP	20	5	25	4	2	2	17	25

*Total number of nonfatal cardiac events indicates 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.

Figure 1. Cumulative survival and event-free survival curve for patients with TVD.

ever, MI was the predominant cause of cardiac death (8/12).

Cumulative survival and event-free survival curve (Figure 1): The survival rate was 80.7% at 5 years and 64.2% at 10 years, indicating a poor survival for TVD patients. When cardiac death, AMI, CHF, PTCA, and CABG were all defined as cardiac events, the 5- and 10-year event-free survival rates were 68.5% and 42.1%, respectively.

Cumulative survival curves stratified for myocardial infarction (Figure 2): In the MI group, the 5- and 10-year survival rates were 80.9% and 62.3%, respectively, and in the AP group, the rates were 80.1% and 68.5%, respectively. There were no differences between the two groups.

Survival in relation to the site of infarction in the MI group (Figure 3): The 5- and 10-year survival rates were respectively 75.3% and 55.8% in patients with anterior MI, 82.8% and 58.2% in patients with inferior MI, and 100% and 100% in patients with posterior MI. Although the survival of patients with posterior MI

Figure 2. Cumulative survival curves for patients according to the presence or absence of myocardial infarction. AP = angina pectoris; MI = myocardial infarction.

Figure 3. Cumulative survival curves for patients with myocardial infarction in relation to the location of infarction

was better, there were no statistically significant differences between the three groups.

Left ventricular ejection fraction (EF) and survival (Figure 4): The relationship between cumulative survival rate and EF was assessed in the MI group. The patients were divided into 3 groups ($\geq 60\%$, 41–59%, and $\leq 40\%$) and the survival rates were compared. The 5- and 10-year survival rates were respectively 93.8% and 73.8% in the patients with an EF $\geq 60\%$, 78.2% and 60.1% in the patients with an EF of 41–59%, and 62.4% and 45.5% in the patients with an EF $\leq 40\%$. Thus, the survival of TVD patients with an EF $\geq 60\%$ was relatively good, whereas the survival rate was significantly lower for patients with an EF $\leq 40\%$.

Survival and chronic total occlusion (CTO) (Figures 5, 6): In the MI group,

Figure 4. Cumulative survival curves for patients with myocardial infarction according to the ejection fraction. EF = ejection fraction.

Figure 5. Cumulative survival curves for patients according to the presence or absence of chronic total occlusion in the AP group. CTO = chronic total occlusion.

the 5- and 10-year survival rates were 78.1% and 55.6% for 97 patients with CTO. These survival rates were lower than those of 83.0% and 62.5% in 40 patients without CTO, although no significant difference was found between the two groups (Figure 5). In the AP group, the 5- and 10-year survival rates were 73.4% and 62.9% for 32 patients with CTO and these survival rates were lower than those of 84.4% and 64.3% in 28 patients without CTO, although there was no significant difference (Figure 6). Survival rates were also compared between patients with and without CTO of the left anterior descending artery, but no significant differences were found in either the MI or AP groups.

Survival and the number of chronic totally-occluded arteries (Figures 7, 8):

In the MI group, the 5-year survival rate was 53.3% for patients with CTO of 3 vessels. This rate was significantly lower than that of 76.0% in patients with CTO of 2 vessels and 79.6% in patients with CTO of a single vessel, whereas the 10-year survival rates showed no significant differences between these 3 groups

Figure 6. Cumulative survival curves for patients according to the presence or absence of chronic total occlusion in the MI group.

Figure 7. Cumulative survival curves in relation to the number of totally-occluded arteries in the AP group

Figure 8. Cumulative survival curves in relation to the number of totally-occluded arteries in the MI group

(53.3%, 50.7%, and 55.9%, respectively) (Figure 7). In the AP group, no patient had CTO of 3 vessels. The 5- and 10-year survival rates were 34.3% and 34.3% for patients with CTO of 2 vessels, and these rates were significantly lower than those of 87.3% and 73.9% in patients with CTO of a single vessel. Thus, survival decreased significantly with an increase of the number of totally-occluded vessels in the AP group (Figure 8).

DISCUSSION

We have previously reported that the prognosis of coronary artery disease treated by medical therapy is generally better in Japanese patients than in American and European patients.¹⁰ We have also reported that left ventricular function and the number of diseased coronary arteries are important prognostic determinants of coronary artery disease.¹⁰ In the present study, we clarified the outcome of medical therapy for TVD and investigated differences in the prognosis of TVD in relation to MI, left ventricular function, and the presence of CTO.

In the United States and Europe there have been many reports of a poor outcome when TVD is treated by medical therapy.^{1-3,11,12} In Japan, the outcome of TVD treated medically has been evaluated in only a few small studies, and the reported 5-year survival rates vary greatly from 62% to 88%.⁴⁻⁷ The 5- and 10-year survival rates obtained in the present study are consistent with those recently reported by the National Cardiovascular Center⁶ and are thought to be representative of the survival of Japanese TVD patients. Our results are better than the 72% reported for the 5-year survival rate reported by Duke University,¹² but medical therapy for patients with TVD is obviously inferior to CABG (99% at 5-years and 92% at 10-years, respectively) as we reported previously.¹³

The incidence of nonfatal MI in our TVD patients was lower than that

reported in patients with single-vessel disease (SVD) and double-vessel disease (DVD).¹⁰⁾ This may be because MI is more often fatal in TVD and it is less common for these patients to survive a heart attack. This is also supported by the finding that sudden death was the main cause of death in our patients with TVD.

The outcome of TVD was similarly unfavorable irrespective of the presence/absence of MI. Anterior infarction has been reported to be a poor prognostic factor.¹⁴⁾ Although the present study also showed a lower survival rate for patients with anterior MI, there were no significant differences between the groups classified by the site of infarction, probably because of the small size of the population studied.

The incidence of cardiac events defined as cardiac death and nonfatal MI was 39.9% after a mean follow-up period of 8.4 years, and the annual attrition rate was 4.7%. This incidence was higher than those we previously reported for SVD and DVD, but it was much lower than the 46% reported for TVD by Harris after a follow-up period of 5 years.¹⁵⁾

The 5-year survival rate was a relatively favorable 93.8% in TVD patients who had an EF $\geq$ 60%, even though they were treated by medication only. However, their 10-year survival rate decreased to a level similar to that in patients with an EF $<$ 60%. Sanz also reported a favorable prognosis in TVD patients with an EF $\geq$ 50%.¹⁶⁾ Thus, there is a difference in the prognosis of TVD according to the EF, suggesting that it is an important prognostic factor in coronary artery disease as reported previously.^{3,11)}

In patients with CTO, revascularization by PTCA is not as successful as that achieved by CABG, and PTCA is often followed by restenosis.^{17,18)} However, it has not yet been clarified how the prognosis of coronary artery disease in patients with TVD is affected by the presence of CTO.^{19,20)} A previous study showed that CTO is a more important prognostic factor than EF in patients with TVD and myocardial infarction, although it was performed in only a small number of patients.⁷⁾ The present study showed no difference in the prognosis of TVD in relation to the presence of CTO as well as the presence/absence of CTO of the left anterior descending artery. In the AP group, the survival rate was decreased as the number of arteries with CTO increased. In the MI group, the survival rate was not affected by the presence of CTO or the number of CTO, but was affected by the EF. This difference of prognostic factors between the EF and CTO in patients with TVD should be studied further.

This study was conducted retrospectively and thus had a number of limitations as mentioned previously.¹⁰⁾ There may be some bias in the selection of subjects. The 75 patients excluded from the present study were treated soon after the initiation of surgery at our hospital, and they were not necessarily more severely ill than the present subjects. In fact, they had rather good left ventricular

function and distal run-off in comparison with the present subjects. Most of the present patients received treatment prior to the introduction of surgery. Their disease varied in severity, ranging from those requiring surgery under current indications to inoperable severe cases. We consider that the study is minimally biased in relation to the subjects.

It showed that TVD with poor LV function ($EF < 60\%$) had a poor long-term outcome with medical treatment, suggesting that aggressive revascularization by PTCA or CABG may be needed in such patients. Although the 5-year survival rate in patients with good left ventricular function ($EF \geq 60\%$) was relatively good, their long-term (10 year) survival rate with medical treatment was as low as that in patients with an $EF < 60\%$, so even patients with good left ventricular function should be carefully monitored and undergo revascularization as necessary.

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