

Clinical and prognostic features in asymptomatic and symptomatic patients with arteriosclerosis obliterans

Hiromichi Ohsaka, Kazunori Shimada, Kosuke Fukao, Eiryu Sai, Yoshifumi Fukushima, Hiroshi Masuda, Kuniaki Hirose, Takuma Yoshihara, Rie Matsumori, Makoto Hiki, Takashi Kiyonagi, Atsumi Kume, Haruyo Yamashita, Tetsuro Miyazaki, Hiroyuki Daida

Department of Cardiology, School of Medicine, Juntendo University, Tokyo, Japan
Email: shimakaz@juntendo.ac.jp

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ABSTRACT

Background: Patients with arteriosclerosis obliterans (ASO) often have co-existing atherosclerotic diseases. The purpose of this study was to examine the clinical features of patients with ASO, including the overlap of atherosclerotic risk factors, characteristics of cardiovascular events, and clinical prognosis. **Method:** We enrolled 205 consecutive patients who had ankle brachial index (ABI) of ≤ 0.9 between January 2008 and December 2009. Fontaine (F) classification and clinical background were evaluated and clinical events including mortality and major adverse cardiocerebrovascular events (MACCEs) were determined. **Results:** There was a high prevalence of each risk factor. Sixty-five percent of subjects had three or more of the four overlapping risk factors, including hypertension, diabetes, dyslipidemia, and smoking. After a maximum follow-up of 800 days, the incidence of MACCEs and mortality was 46% and 10%, respectively. We divided the patients into two groups according to the presence of ASO symptoms (F1 and F2-4) and compared the incidence of events. The incidence of MACCEs and mortality in the F2-4 group was significantly higher than that in the F1 group ($P = 0.048$, $P = 0.044$, respectively). After excluding lower extremity revascularization, coronary artery disease was a common cause of MACCEs, and the mortality rates after MACCEs increased in a stepwise manner according to F classification severity ($P = 0.028$). **Conclusion:** Patients with ASO had overlapping coronary risk factors and a high incidence rate of cardiovascular events. The incidence of coronary events was common, especially in symptomatic patients, and the mortality rates after MACCEs were high in accordance with F classification severity.

Keywords: Arteriosclerosis Obliterans; Fontaine Classification; Risk Factor; Mortality; Cardiocerebrovascular Event

1. INTRODUCTION

The prevalence of atherosclerotic risk factors continues to increase throughout the world, including Japan, because of the spread of western lifestyle habits [1,2]. There has been a concomitant increase in atherosclerotic diseases, and heart disease and stroke have become the #2 and #3 causes of death in Japan according to 2010 statistics [3]. In addition, the Japanese population is aging rapidly [4]. Therefore, it is believed that the number of patients with arteriosclerosis obliterans (ASO) has been increasing. Epidemiological studies in the general population have shown the incidence of ASO to be 1% in people aged below 60% and 3.4% in people aged 65 or more [5]. Furthermore, the estimated number of patients with ASO in Japan, including asymptomatic patients, ranges from 500,000 to 800,000 [6-8]. Patients with ASO have also been shown to have a high risk of developing other atherosclerotic diseases [9-11]. Although, there have been previous studies of cardiovascular events and clinical prognosis in patients with ASO [9,12,13], it is likely that circumstances regarding the overlapping of various lifestyle-related risk factors and the incidence of cardiovascular events are changing over time. Thus, it is important to examine the clinical and prognostic features of patients with ASO indicating the recent clinical situation of various novel drug treatments for hypertension (HT), diabetes mellitus (DM), and dyslipidemia (DL). In addition, there have been no reports to date on the mortality rates of patients with ASO after the incidence of cardiovascular events.

Thus, the purpose of this study was to examine the clinical features of patients with ASO, including the overlapping of atherosclerotic risk factors, characteristics of cardiovascular events, and clinical prognosis.

2. METHODS

2.1. Subjects

Two hundred and five consecutive patients with an ankle

brachial index (ABI) of ≤ 0.9 measured using the form ABI/PWV (Omron Colin Co., Ltd, Tokyo) were enrolled between January 2008 and December 2009. Patients with acute coronary syndrome (ACS) within the last three months, those hospitalized due to congestive heart failure (CHF), those with active infection and systemic inflammatory diseases, and those with scheduled lower extremity revascularization were excluded from the study. Subjects were classified according to the Fontaine (F) classification into F1, no symptoms in the lower extremities; F2, intermittent claudication; F3, pain at rest, and F4, skin ulceration and/or necrosis of lower limbs [14]. DL was diagnosed in patients undergoing treatment having total cholesterol (TC) levels of 220 mg/dL or higher, low-density lipoprotein cholesterol levels (LDL-C) of 140 mg/dL or higher, high-density lipoprotein cholesterol (HDL-C) levels of less 40 mg/dL or lower, or triglycerides (TG) levels of 150 mg/dL or higher [15]. HT was diagnosed in patients undergoing treatment and having a blood pressure of 140/90 mmHg or higher [16]. DM was diagnosed in patients undergoing treatment and in those with hyperglycemia by two or more tests with blood glucose levels of 200 mg/dL or higher and an HbA1c reading of 6.5% or higher (Japan Diabetes Society 6.1%) [17]. Estimated glomerular filtration rate was calculated for chronic kidney disease (CKD) according to guidelines [18]. Furthermore, antiplatelet agents and prostaglandin properties were also examined in drug treatment histories in addition to the above mentioned drugs. Written informed consent was obtained from all subjects and the ethics committee of the institution approved this study.

2.2. Major Adverse Cardiocerebrovascular Events (MACCE)

We observed the clinical course of the subjects for a maximum of 800 days. MACCEs were defined as cardiovascular deaths, non-fatal myocardial infarction, unstable angina, coronary revascularization, admission for stroke, heart failure requiring hospitalization, lower extremity amputation, and lower extremity revascularization.

2.3. Statistical Analysis

Student's *t*-test, Welch's *t*-tests, or Mann-Whitney *U*-test was used for comparison of clinical data, and the χ^2 test was used for ratio comparison. ANNOVA test was used for comparison of three or more groups. JUMP8.0 MDSU statistical software (SAS Institute, Cary, NC, USA) was used for statistical analysis of survival curves and results were verified using the paired *t*-tests or Wilcoxon test. Data was expressed as mean \pm standard deviation and significant difference determined with a $P < 0.05$ was considered to be statistically.

3. RESULTS

3.1. Comparison of Clinical Features

The clinical features of the 205 subjects are shown in **Table 1**. The average age of the subjects was 71 years \pm 10 years, and 78% of them were male. They average body mass index was $22.1 \text{ kg/m}^2 \pm 3.3 \text{ kg/m}^2$. The prevalence of HT, DM and DL was 84%, 54%, and 77%, respectively. Twenty-four percent were current smokers and 44% were former smokers. Twenty-seven patients had undergone dialysis. The prevalence of myocardial infarction, percutaneous coronary intervention, and coronary aorta bypass grafting was 30%, 29%, and 23%, respectively. Percentages of F1, F2, F3, and F4 were 38%, 44%, 12%, and 6%, respectively. Significant differences in ABI ($P < 0.001$), TC ($P = 0.045$), HDL-cholesterol ($P = 0.027$) and prostaglandin administration ($P = 0.015$) were observed among the four groups.

3.2. Risk Factor Merger Rate and Multiplicity

Figure 1 shows the rates of overlap among HT, DM, DL and smoking (SM). Overlapping of all four risk factors was observed in 23%, three risk factors in 65% and two risk factors in 86% of the subjects. Except a frequent history of SM in males, there was little gender difference in prevalence of the four factors.

3.3. Clinical Prognosis

Figure 2 demonstrates the incidence of MACCEs and total mortality. Forty-six percent of subjects suffered a MACCEs with lower extremity revascularization being the most common (39%), followed by CHF (23%), CAD (21%), and cerebrovascular disease (CVD; 11%). Twenty-one patients died (10%) because of CAD (33%), CHF (24%), CVD (19%). There was a significant difference in the Kaplan-Meier curves of MACCEs between the four F groups. Because there were few F4 subjects, a comparison between the asymptomatic ASO group (F1) and symptomatic ASO group (F2-4) is shown in **Figure 3**. The F2-4 group had a significantly higher incidence of MACCEs than the F1 group (log-rank test, $P = 0.048$). Similarly, there was a significant difference in Kaplan-Meier mortality event curves between the four F groups (logrank test: $P < 0.001$, Wilcoxon test: $P < 0.001$). The F2-4 group had a significantly higher incidence of mortality than the F1 group (log-rank test, $P = 0.044$).

3.4. Mortality Rate after Cardiovascular Events

Figure 4 shows the details of the cardiovascular events occurring in the four F groups. The proportion of lower extremity revascularization in groups F2, F3 and F4 was 51%, 33%, and 80%, respectively. In analysis that excluded lower extremity revascularization, the incidence of CAD and mortality increased with F classification severity.

Table 1. Patient characteristics. Data are presented as means \pm SDs or percentages. F: Fontaine, HDL: high-density lipoprotein, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate, hsCRP: high sensitive C-reactive protein, JDS; Japan Diabetes Society.

	Total	F1	F2	F3	F4	P
Number	205	78	90	25	12	
Age, years	71 \pm 10	70 \pm 11	72 \pm 9	73 \pm 8	66 \pm 13	0.214
Male (%)	160 (78)	58 (74)	73 (81)	20 (80)	9 (75)	0.745
Body mass index, kg/m ²	22.1 \pm 3.3	22.2 \pm 3.5	22.0 \pm 3.3	22.5 \pm 2.8	21.0 \pm 2.6	0.646
Hypertension (%)	173 (84)	68 (87)	73 (81)	20 (80)	12 (100)	0.286
Diabetes mellitus (%)	113 (55)	41 (53)	48 (53)	15 (60)	8 (67)	0.756
Dyslipidemia (%)	158 (77)	57 (73)	73 (80)	20 (80)	8 (67)	0.495
Smoking history						
Current (%)	50 (24)	14 (18)	26 (29)	6 (24)	4 (30)	0.462
Former (%)	92 (45)	32 (41)	42 (47)	16 (62)	2 (18)	0.098
History of coronary artery disease						
Myocardial infarction (%)	62 (30)	27 (33)	24 (26)	6 (22)	5 (45)	0.439
Percutaneous coronary intervention (%)	59 (29)	22 (28)	27 (30)	9 (37)	1 (10)	0.495
Coronary aorta bypass grafting (%)	47 (23)	21 (27)	19 (20)	3 (11)	4 (36)	0.289
History of peripheral revascularization						
Peripheral bypass (%)	29 (14)	9 (11)	18 (20)	3 (11)	0 (0)	0.168
Peripheral intervention (%)	55 (27)	19 (25)	24 (27)	12 (47)	0 (0)	0.018
History of cerebrovascular disease (%)	61 (30)	28 (36)	22 (24)	8 (32)	3 (25)	0.421
Hemodialysis (%)	27 (13)	8 (10)	11 (12)	5 (20)	3 (25)	0.580
Ankle brachial index	0.70 \pm 0.14	0.75 \pm 0.12	0.66 \pm 0.14 *	0.65 \pm 0.12 *	0.76 \pm 0.13	<0.001
Brachial-ankle pulse wave velocity, cm/s	1688 \pm 542	1601 \pm 499	1763 \pm 548	1493 \pm 446	1479 \pm 586	0.233
Laboratory data						
Total cholesterol, mg/dl	178 \pm 52	173 \pm 34	189 \pm 66	166 \pm 39	157 \pm 41	0.045
Triglyceride, mg/dl	144 \pm 216	133 \pm 69	171 \pm 321	101 \pm 42	111 \pm 45	0.436
HDL cholesterol, mg/dl	47 \pm 16	43 \pm 13	50 \pm 17	49 \pm 19	44 \pm 15	0.027
LDL cholesterol, mg/dl	102 \pm 30	104 \pm 27	105 \pm 30	95 \pm 32	91 \pm 36	0.231
Fasting plasma glucose, mg/dl	96 \pm 25	101 \pm 27	94 \pm 26	91 \pm 21	92 \pm 17	0.374
HbA1c, % (JDS)	6.5 \pm 1.2 (6.1 \pm 1.2)	6.5 \pm 1.1 (6.1 \pm 1.1)	6.4 \pm 1.0 (6.0 \pm 0.9)	6.9 \pm 1.8 (6.5 \pm 1.9)	6.5 \pm 1.3 (6.1 \pm 1.3)	0.473
eGFR, ml/min/1.73m ²	54 \pm 28	49.5 \pm 26.9	55.6 \pm 26.1	58.8 \pm 30.5	59.6 \pm 43.1	0.373
hsCRP, mg/dl	0.692 \pm 1.934	0.562 \pm 1.653	0.844 \pm 2.305	0.760 \pm 2.000	0.748 \pm 1.448	0.934
Brain natriuretic peptide, pg/dl	217 \pm 358	260 \pm 353	192 \pm 386	144 \pm 221	316 \pm 470	0.374
Medications						
Aspirin (%)	150 (73)	55 (71)	68 (76)	19 (76)	8 (64)	0.803
Ticlopidine (%)	29 (14)	12 (16)	14 (16)	2 (8)	1 (9)	0.735
Clopidogrel (%)	38 (19)	13 (17)	15 (17)	8 (32)	2 (18)	0.345
Cilostazol (%)	50 (25)	14 (18)	25 (28)	8 (32)	3 (27)	0.395
Prostaglandin (%)	60 (29)	12 (15)	35 (39)	11 (44)	2 (18)	0.009
Calcium channel blockers (%)	82 (40)	28 (36)	39 (43)	10 (40)	5 (45)	0.811
Renin-angiotensin related agents (%)	117 (57)	48 (62)	50 (56)	13 (52)	6 (50)	0.747
Beta blockers (%)	74 (36)	30 (39)	26 (29)	11 (44)	7 (55)	0.203
Statin (%)	101 (49)	33 (42)	52 (58)	12 (48)	4 (36)	0.159
Insulin (%)	43 (21)	15 (19)	18 (20)	7 (28)	3 (27)	0.765

P value; ANOVA of continuous variable, χ^2 test of Nominal scales, * $p < 0.05$ vs F4; Dunnett test.

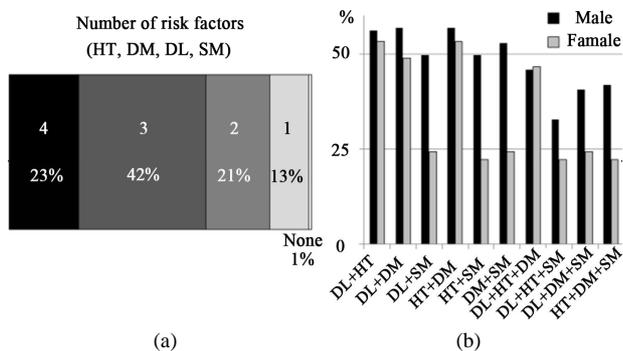


Figure 1. Prevalence of overlapping risk factors. There was overlap of all four risk factors (HT, DM, DL, and SM) in 23% of subjects, three or more risk factors in 65% of subjects, and two or more risk factors in 86% of subjects. A trend of more frequent history of SM was evident in males, but there was little gender difference in HT, DM, or DL. HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; SM, smoking.

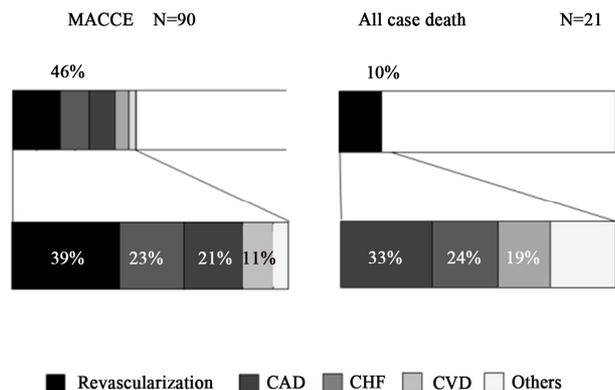


Figure 2. Prevalence and cause of MACCEs and death. Forty-six percent of subjects suffered a MACCE. Among these, lower extremity revascularization was the most common (39%), followed by CHF (23%), CAD (21%) and CVD (11%). Twenty-one patients died (10%) due to CAD (33%), CHF (24%), and CVD (19%). F, Fontaine; MACCEs, major adverse cardiocerebrovascular events; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease.

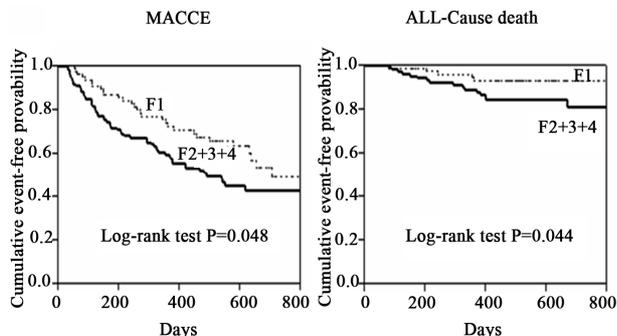


Figure 3. Kaplan-Meier curves of MACCEs and mortality. The F2-4 groups had a significantly higher incidence of MACCEs and total mortality than that in the F1 group (log-rank test, $P = 0.048$ and $P = 0.044$ respectively). F, Fontaine; MACCEs, major adverse cardiocerebrovascular events.

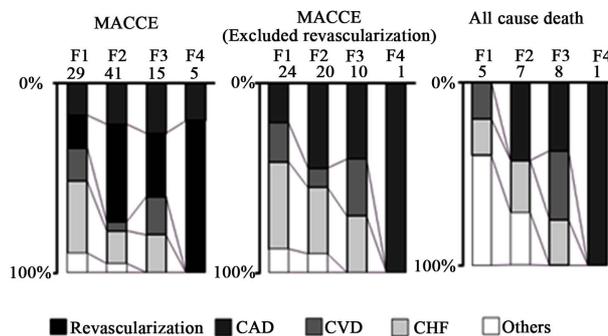


Figure 4. Primary causes of MACCEs and mortality in different F classification after excluding lower extremity revascularization, the incidence of CAD and mortality increased with F classification severity. F, Fontaine; MACCEs, major adverse cardiocerebrovascular events; CAD, coronary artery disease; CHF, congestive heart failure; CVD, cerebrovascular disease.

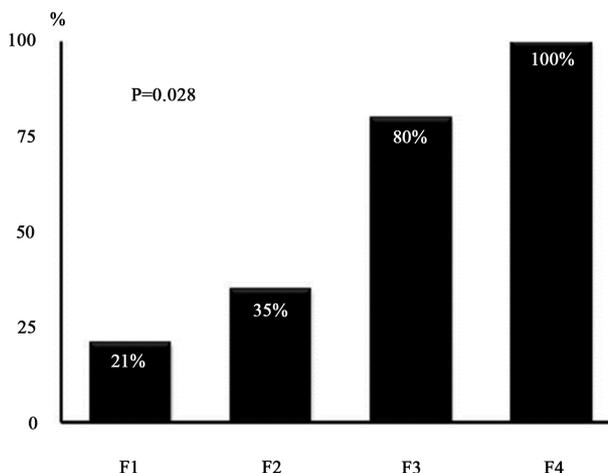


Figure 5. Lethality rates of each F classification group after cardiovascular events. The mortality rates after the onset of cardiovascular events excluding lower extremity revascularization significantly increased with F classification severity. F, Fontaine.

Figure 5 shows the mortality rates in the four F groups after the incidence of cardiovascular events excluding lower extremity revascularization. The mortality rates after cardiovascular events, excluding lower extremity revascularization, significantly increased with F classification severity ($P = 0.028$).

4. DISCUSSION

Patients with ASO had a high prevalence of overlapping coronary risk factors and a high incidence of cardiovascular events. The incidence of coronary events was common, especially in symptomatic patients, and the mortality rates after MACCEs were high in accordance with F classification severity.

In this study, no significant differences in any risk factors were observed among the F groups except for TC

and HDL-C. However, the prevalence of patients with high TC levels and low HDL-C levels was not necessarily common in the F3 and F4 groups. Thus, these factors cannot explain why MACCEs and total mortality in the symptomatic F2-F4 groups were higher than those in the F1 group. One possible reason is that the high prevalence of overlapping risk factors may be associated with the onset of clinical events. Indeed, the overlapping rate of three or four of these factors in the MACCEs occurrence and mortality groups was higher compared to the non-MACCEs occurrence and survival groups (data not shown). An increased risk of cardiovascular events in patients with atherosclerotic disease along with overlapping of risk factors has been reported in previous studies [5,9,19]. Overlap of risk factors not only accelerates the progression of systemic atherosclerosis and lower extremity peripheral vascular disease but also increases the combined rate of CAD and CVD, resulting in high susceptibility to polyvascular disease. Furthermore, CKD complications including end-stage renal disease and impairment of respiratory function associated with SM are related to the incidence of MACCEs, and also correlated with poor prognosis [9,11,20]. The second possible reason involves the recent circumstances of drug treatment. The TASCII guidelines recommended that lipid levels should be controlled by decreasing LDL-C levels to less than 100 mg/dl (or 70 mg/dl in patients with CAD), increasing HDL-C levels to 40 mg/dl or above, and decreasing TG levels to less than 140 mg/dl [21-25]. Similarly, it is recommended that blood pressure should be controlled at a level of less than 140/90 mmHg (or less than 130/80 mmHg for patients with DM or renal failure) and DM should be controlled at HbA1c levels of less than 7% [17]. It is necessary to examine the details of the type of drug treatment and dosage in these respective groups in the future. Furthermore, the possibility that the extent of lifestyle improvement in relation to various risk factors is associated with improved prognosis is also a possibility to consider. However, this study did not include any data on nutrition and exercise habits and further examination is needed to investigate these issues.

The cause of death in 7 of 21 subjects who died during this observation period was CAD. Coronary events, excluding lower extremity revascularization, were the common MACCEs. Furthermore, coronary events were also the most common cause of total mortality. It was also clear that the mortality rate after events, excluding lower extremity revascularization, were the common MACCEs. Furthermore, coronary events were also the most common cause of total mortality. It was also clear that the mortality rate after the incidence of cardiovascular events (excluding lower extremity revascularization) increased with F classification severity, which is in agreement with the results of a previous study [26]. However, the pre-

sent study demonstrated a novel finding that mortality after cardiovascular events increased a stepwise manner with F classification severity. As mentioned above, the risk of polyvascular disease including CAD and the clinical severity of complications may increase along with F classification severity. These combined damages in various organs may be involved in this adverse process. Furthermore, patients with severe ASO could be restricted in their daily living activities, which may mask severe CAD symptoms [27,28]. In addition, it is possible that typical symptoms of CAD may not be readily evident in cases with combined DM or in older subjects [29,30]. Therefore, aggressive screening for CAD is required in patients with ASO, especially in F-2 or above.

5. LIMITATIONS

This study had several limitations. First, it was a single center study with a small sample size. Second, it is possible that the high multiplicity of risk factors and subsequent high rate of cardiovascular events may be because of selection bias. ABI was measured at the discretion of each physician. However, patients with acute cardiovascular disease and those scheduled for lower extremity revascularization were excluded from this study. Third, hemodialysis patients with a generally poor prognosis were included in this study. We are planning to examine clinical prognosis in patients with ASO and hemodialysis in a relatively large study in the near future. Fourth, the proportion of elderly subjects was relatively high. It may be one of the reasons that BMI levels were relatively low. The combination rate of metabolic syndrome associated with visceral obesity may be different in younger subjects and further studies are needed to assess this possibility.

6. CONCLUSION

Patients with ASO had high prevalence of overlapping coronary risk factors and a high incidence rate of cardiovascular events. Such cases with combined defects were example of so-called polyvascular disease, and therefore, required comprehensive management of risk factors. In addition, the incidence of coronary events was common in symptomatic patients and the mortality rates after MACCEs were also high in accordance with F classification severity. Thus, aggressive screening for CAD is required in patients with ASO, especially those in symptomatic for ASO.

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