学位論文

Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: A report from the Angina Pectoris-Myocardial Infarction Multicenter Investigators in Japan
（急性心筋梗塞を発症した若年女性における特発性冠動脈解離の予後への影響：狭心症・心筋梗塞研究会からの報告）

中島 啓裕
Takahiro Nakashima

熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

指導教員

安田 聡 客員教授
熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学

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著 者 名　：　中 島　啓 裕
Takahiro　Nakashima

指導教員名　：　熊本大学大学院医学教育部博士課程医学専攻循環器先進医療学 安田 聡 客員教授

審査委員名　：　循環器内科学担当教授　辻田 賢一
救急・総合診療医学担当教授　笠岡 俊志
心臓血管外科学担当教授　福井 寿啓
分子遺伝学担当教授　尾池 雄一

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Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: A report from the Angina Pectoris–Myocardial Infarction Multicenter Investigators in Japan

Takahiro Nakashima [a,b], Teruo Noguchi [a], Seiichi Haruta [c], Yusuke Yamamoto [d], Shuichi Oshima [e], Koichi Nakao [f], Yasuyo Taniguchi [g], Junichi Yamaguchi [h], Kazufumi Tsuchihashi [i], Atsushi Seki [j], Tomohiro Kawasaki [k], Tatsuro Uchida [l], Nobuhiro Omura [m], Migaku Kikuchi [n], Kazuo Kimura [o], Hisao Ogawa [a,b,p], Shunichi Miyazaki [q], Satoshi Yasuda [a,b,*]

[a] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
[b] Department of Advanced Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[c] Division of Cardiology, Fukuyama Cardiovascular Hospital, Fukuyama, Japan
[d] Division of Cardiology, Saiseikai Fukuoka General Hospital, Fukuoka, Japan
[e] Division of Cardiology, Kumamoto Central Hospital, Kumamoto, Japan
[f] Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, Kumamoto, Japan
[g] Department of Cardiology, Hyogo Brain and Heart Center, Himeji, Japan
[h] Department of Cardiology, The Heart Institute of Japan, Tokyo Women's Medical University, Tokyo, Japan
[i] Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan
[j] Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan
[k] Cardiovascular Center, Shin-Koga Hospital, Kurume, Japan
[l] Division of Cardiovascular Medicine, Sendai Cardiovascular Center, Sendai, Japan
[m] Nakada Internal Medicine Clinic, Saitama, Japan
[n] Department of Cardiovascular Medicine, Dokkyo Medical University School of Medicine, Mibu, Japan
[o] Department of Cardiology, Yokohama City University Medical Center, Yokohama, Japan
[p] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[q] Division of Cardiology, Department of Internal Medicine, Kinki University Faculty of Medicine, Sayama, Japan

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ABSTRACT

Background: We sought to compare the prognosis of patients with spontaneous coronary artery dissection (SCAD) and atherosclerosis as the cause of acute myocardial infarction (AMI), especially in young females.
Methods and results: A total of 20,195 patients with AMI at 20 institutions between 2000 and 2013 were retrospectively studied. Major adverse cardiac event (MACE: cardiac death, AMI or urgent revascularization) was the endpoint. The overall prevalence of SCAD was 0.31% (n = 63; female, 94%). SCAD developed following emotional stress in 29% of patients. Revascularization was performed in 56% (35 of 63 patients), and SCAD recurrence developed in the originally involved vessel in 6 of 35 patients with revascularization, compared to none among 28 patients after conservative therapy ($p = 0.002$). We compared the clinical characteristics of young female AMI patients aged ≤50 years in the SCAD (n = 45) and no-SCAD groups (atherosclerotic AMI, n = 55). During a median follow-up of 50 months, SCAD recurred in 27% of patients, of which 42% was in the first 30 days. Kaplan–Meier analysis showed a significantly higher incidence of MACE in the SCAD group compared to the no-SCAD group (hazard ratio, 6.91; 95% confidence interval, 2.5 to 24.3; $p < 0.001$), although the rate of successful percutaneous coronary intervention for SCAD was as high as 92%.
Conclusions: Young female patients with SCAD represent a high-risk subgroup of patients with AMI and require close follow-up.

1. Introduction

Spontaneous coronary artery dissection (SCAD) remains a rare but challenging clinical entity, with an estimated prevalence ranging from 0.07% to 1.1% [1,2]. Recent large single center cohort studies of SCAD reported that it could occur in both younger and older females [3,4].

* Corresponding author at: Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita 565-8565, Japan.
E-mail address: yasuda.satoshi.hp@mail.ncvc.go.jp (S. Yasuda).

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Moreover, the rate of SCAD recurrence in these cohorts were 17% and 13%, respectively, which was unexpectedly higher than those reported in previous studies [2,5,6]. On the other hand, SCAD has been traditionally considered to occur in young females with minimal atherosclerotic risk factors and not as part of a broader clinical spectrum that includes older patients with coronary artery disease (CAD) [7]. However, there were no systematic study focusing on young female and their prognosis remains unclear, as reported in the recent two large cohort studies [3,4]. Hence, in this study, we focused on the short- and long-term prognosis of young female patients aged less than 50 years with SCAD.

The present study involves a large series of patients who underwent coronary angiography (CAG) due to acute myocardial infarction (AMI) that were enrolled by investigators at multiple centers by the Angina Pectoris–Myocardial Infarction (AP–MI) Study Group [8] that uses conservative and interventional strategies for SCAD in actual clinical practice. We sought to 1) evaluate the prevalence and the short- and long-term outcomes of SCAD, 2) determine the recurrence rate of SCAD, and 3) compare the prognosis of young female patients with non-atherosclerotic AMI due to SCAD and those with atherosclerotic AMI.

2. Methods

2.1. Study population of the multicenter cohort and the definition of SCAD

From January 2000 to December 2013, a total of 20,195 patients with AMI were admitted to 20 cardiovascular institutions in Japan by AP-MI investigators (Appendix A) [8]. SCAD was defined as medial dissection or intramural hematoma without atherosclerotic changes detected by CAG, intravascular ultrasonography (IVUS), or optical coherence tomography (OCT) before any catheter-based intervention [9–11]. We defined SCAD according to the report from Saw et al. [4]. Briefly, their classification system grades coronary dissection on the basis of angiographic appearance into three types: type 1, pathognomonic contrast dye staining in the arterial wall with multiple radiolucent lumens; type 2, diffuse smooth narrowing with mild stenosis; and type 3, mimicking atherosclerosis with focal or tubular stenosis. In all cases in whom type 2 or 3 SCAD was suspected based on angiography, we confirmed the presence of intramural hematoma or a double lumen by intracoronary imaging with IVUS or OCT. The presence of an intimal flap was not necessary for diagnosis. In the present study, the angiographic data of all patients diagnosed with SCAD at each center were collected at the core laboratory of the National Cerebral Cardiovascular Center in Japan and confirmed independently by at least 2 interventional cardiologists. Percutaneous coronary intervention (PCI)-related dissection, post-traumatic coronary artery dissection, and atherosclerotic-related dissection were excluded [12]. Clinical, angiographic, laboratory, and treatment data were collected to clarify the characteristics of and precipitating factors in patients with SCAD.

Since SCAD outside of the setting of atherosclerosis has a relatively younger and more female predominance, our analysis focused on younger female AMI patients with SCAD. Among 20,195 patients with AMI, there were a total of 130 female AMI patients aged 50 years or younger. After exclusion of patients with vasospastic angina pectoris (n = 13), coronary artery embolism (n = 10), systemic lupus erythematosus (n = 3), Kawasaki disease (n = 1), Vasculo-Behcet's disease (n = 1), and other (n = 2), the remaining 100 patients were ultimately included in additional analyses. This retrospective study was conducted in accordance with the 1975 declaration of Helsinki and approved by the institutional review board of each site and informed consent was obtained from each patient.

2.2. Data collection and definitions

Demographic and clinical data such as potential etiologic factors, coronary risk factors, clinical presentation, involved vessel distribution, and initial management strategy were collected. Emotional stress and extreme physical activity were reviewed from medical records. In-hospital and long-term outcomes were determined through medical record and angiographic review. When necessary, a mailed questionnaire and telephone follow-up were also used. Endpoints included major adverse cardiac events (MACE), which consist of cardiac death, non-fatal AMI or urgent revascularization. Recurrent SCAD was defined as the development of de novo dissection, which is distinct from potential propagation of primary SCAD associated with acute coronary syndrome in the initial SCAD lesion within one week of the index event.

AMI was defined according to the following inclusion criteria: (1) continuous chest pain lasting >30 min, (2) new left bundle branch block or ST-segment changes in 2 or more contiguous leads on the 12-lead electrocardiogram (ECG), and (3) subsequent increase in serum creatine kinase (CK) to more than twice the upper limit of normal [13,14]. ST-elevation myocardial infarction (STEMI) was defined as an AMI with new ST elevation at the J-point in 2 contiguous leads with the following cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V_2–V_3, or ≥0.1 mV in other leads [14].

PCI was performed when a patient presented with evidence of ongoing ischemia such as prolonged chest pain, ischemic ST changes, or hemodynamic instability. PCI was considered successful when improvement from Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow at baseline to TIMI grade 3 flow was achieved. A procedure was considered technically complicated when there was an unexpected need for additional stenting for dissection propagation or expansion of an intramural hematoma during PCI [15].

2.3. Statistical analysis

Normally distributed continuous variables are presented as means ± standard deviation (SD); they were compared using the *t*-test. Non-normally distributed variables are presented as medians (interquartile range, IQR). They were compared using the Mann–Whitney *U* test. Categorical baseline variables were compared using Fisher's exact test or the chi-squared test as appropriate. Cumulative event-free survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. All p values < 0.05 were considered statistically significant. Statistical analysis was performed with JMP version 10 (SAS Institute Cary, NC).

3. Results

3.1. Prevalence, clinical characteristics, and precipitating factors for SCAD

In the study population occurred AMI, the overall prevalence of SCAD was 0.31% (63 per 20,195 subjects) (Fig. 1, Study 1). Table 1 shows the clinical characteristics of patients with SCAD. Among 63 patients with SCAD, the mean age was 46 ± 10 years and 59 (94%) were female. STEMI was the presenting diagnosis in 87% and non-STEMI in 13%. Cardiogenic shock or cardiac arrest was observed in 10 (16%) patients. Potential precipitating factors, including hormonal, vascular, or shear stress-related factors, were identified in 39 (62%) patients. The most common precipitating factor for SCAD was emotional stress in 18 (29%) patients (illness of a family member, n = 1; argument, n = 3; interrogation at a police station, n = 1; excessive work, n = 8; stress associated with raising children, n = 2; panic attack, n = 1; postoperative stress, n = 1; post-earthquake stress, n = 1). Five (8.1%) patients presented with SCAD during the peripartum period. Among 25 subjects that were screened for fibromuscular dysplasia (FMD) by a combination of computed tomography angiography (CTA), magnetic resonance angiography (MRA), and ultrasonography (n = 23) or ultrasonography alone (n = 2), the prevalence of FMD was 20% (5 of 25 patients), which was the second most frequent precipitating factor. One patient was diagnosed with FMD due to concomitant carotid dissection.

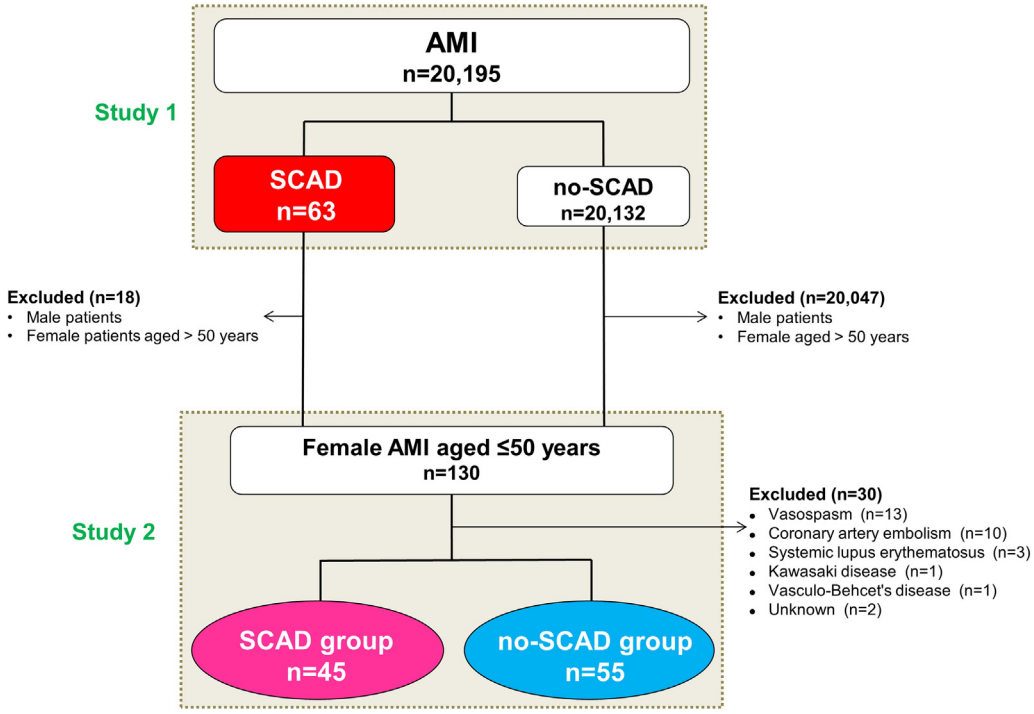

Fig. 1. Flow chart of the study patients. Among an overall cohort of 20,195 cases with acute myocardial infarction (AMI) between 1991 and 2013, we initially studied 63 patients who met the criteria for spontaneous coronary artery dissection (SCAD) (Study 1). We then focused on SCAD in young female AMI patients aged 50 years or younger (n = 45). There were a total of 130 female AMI patients aged 50 years or younger. Following exclusion of patients with: vasospastic angina pectoris, coronary artery embolism, systemic lupus erythematosus, Kawasaki disease, Vasculo-Behcet's disease, and other, the remaining 100 patients were ultimately included for additional analysis (Study 2).

3.2. Angiographic findings and initial management strategies

Table 2 shows the angiographic findings and initial management strategies for the 63 SCAD patients. The left anterior descending artery was the most frequently involved vessel (59%). Multivessel coronary

Table 1
Clinical characteristics, precipitating factors, presentation of SCAD.

	n = 63
Baseline characteristics	
Age, yrs	46 ± 10
Female	59 (94)
BMI, kg/m^2	22.4 ± 4.2
Smoking	20 (32)
Family history	5 (8)
Hypertension	21 (33)
Diabetes mellitus	0
Hyperlipidemia	14 (23)
Chronic kidney disease	0
Presentation	
STEMI	55 (87)
NSTEMI	8 (13)
Cardiogenic shock or cardiac arrest	10 (16)
Concomitant other vessel dissection	1 (2)
Precipitating factors	
Emotional stress	18 (29)
Extreme physical activity	6 (10)
Fibromuscular dysplasia (a total of 24 subjects)[a]	5 (20)
Oral contraceptives	0
Postmenopausal hormone therapy	1 (2)
Peripartum period	5 (8)
Early menopause	3 (5)
Marfan syndrome	1 (2)

Values are n (%) or mean ± SD.
CKD indicates chronic kidney disease, STEMI; ST-elevation myocardial infarction, NSTEMI; non-ST-elevation myocardial infarction.
[a] A total of 24 subjects were screened for fibromuscular dysplasia.

Table 2
Angiographic findings, initial management strategies.

	n = 63
Distribution	
LMT	0
LAD	37 (59)
LCX	4 (6)
RCA	15 (24)
Multi-vessel	7 (11)
Initial TIMI flow grade	
0	27 (44)
1	7 (12)
2	16 (26)
3	12 (19)
Intimal flap	50 (79)
Using intracoronary imaging modality	41 (65)
SCAD lesion characteristics	
Type 1 angiographic SCAD	27 (43)
Type 2 angiographic SCAD	35 (55)
Type 3 angiographic SCAD	1 (2)
Initial management strategy	
Revascularization therapy	35 (56)
PCI	34
CABG	1
Conservative therapy	28 (44)
Details of PCI procedure (n = 34)	
Stent implantation	23 (68)
POBA	11 (32)
Successful PCI	31 (91)
Technically complicated PCI	8 (24)

Categorical variables are expressed as n (%).
LMT indicates left main trunk artery, LAD left anterior descending artery, LCX; left circumflex artery, RCA; right coronary artery, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft, POBA; plain old balloon angioplasty, technically complicated PCI; propagation of dissection, cardiogenic shock or life-threatening arrhythmia during PCI.

dissection was found in 7 (11%) patients, all of whom had 2-vessel dissection. An intimal flap was observed on angiography in 50 (79%) patients. Regarding angiographic appearance of SCAD lesion, [4] type 1 was observed in 43%, type 2 was observed 55% and the remaining 2% was type 3, which were defined by IVUS (n = 38) and OCT (n = 3), respectively. Thirty-five (56%) patients underwent revascularization, while the remaining 28 (44%) patients underwent conservative therapy, including 3 (12%) patients who received fibrinolytics. Revascularization procedures included coronary artery bypass grafting (CABG) in 1 (3%) patient and PCI in 34 (97%) patients. Among patients who underwent PCI (Supplementary Table 1), 32 (91%) had intravascular imaging before PCI (IVUS, n = 30; OCT, n = 2). The overall technical PCI success rate was 91% (31 of 34 patients, including stenting in 23 patients and balloon angioplasty only in 11 patients). Eight of these 34 PCI procedures (24%) were complicated by unanticipated propagation of the dissection flap requiring additional stents to be placed during the intervention. The entire length of the dissection was covered with stents in 12 patients (52%), and only the dissection entry site was covered with stents in 11 patients (48%). The stent diameter/vessel diameter ratio was 1.03 ± 0.16. In 2 patients, it was not possible to pass a wire into the true lumen distally; one patient developed dissection during the intervention with a lower final TIMI flow grade and ultimately required emergent CABG.

3.3. Long-term outcomes in patients with SCAD

3.3.1. SCAD recurrence and MACE

During a median follow-up of 34 months (range, 3 to 160 months) with no loss to follow-up, 4 (6%) patients developed re-infarction due to potential propagation of primary SCAD and 14 (22%) patients developed re-infarction due to SCAD recurrence. Fig. 2 shows the Kaplan–Meier curves for MACE. During follow-up, 1 patient experienced sudden cardiac death and 18 had AMI. The 5-year event rate for MACE in patients with SCAD was 37%. Of the 14 patients with recurrent SCAD, 7 (50%) patients experienced recurrence during the first 30 days after the primary SCAD event. The median interval from the onset of SCAD to the second episode of SCAD was 42 days (range, 1 to 2968 days).

Fig. 3 compares the rate of recurrent SCAD between patients initially managed with revascularization and conservative therapy. The overall incidence of SCAD recurrence was not significantly different between the 2 groups (revascularization, 26% vs. conservative therapy, 21%, p = 0.772). However, 17% (6 of 35 patients) of the revascularization group developed recurrent SCAD in the originally involved PCI-treated vessel, whereas none of patients in the conservative therapy group developed SCAD in the originally involved vessel (p = 0.002). In the conservative therapy group, 19 of 28 (68%) patients had evidence of vessel wall healing on CTA or CAG at a median follow-up of 3.4 months (range, 0.1 to 103 months). Fig. 4A–C shows a representative case in the revascularization group in which recurrent SCAD developed in the originally involved, PCI-treated vessel. Fig. 4D–E shows a representative case in the conservative therapy group, in which vessel injury was spontaneously healed by 6 months after the onset of SCAD.

3.4. Characteristics and prognosis of young female AMI patients with and without SCAD

3.4.1. Clinical characteristics and in-hospital outcomes

Of the 20,195 AMI patients, the prevalence of AMI in women aged 50 years or younger was 0.64% (Fig. 1, Study 2). Fig. 5 shows the causes of AMI in the 130 young female AMI patients. While atherosclerosis was the most frequent cause of AMI (n = 55, 42%), SCAD was the second most frequent cause (n = 45, 35%). Table 3 compares the clinical characteristics of the no-SCAD (i.e., atherosclerosis-associated AMI) and SCAD groups. Compared with the no-SCAD group, the SCAD group had a lower prevalence of hypertension (p < 0.001), diabetes mellitus (p < 0.001), and hyperlipidemia (p < 0.001). Consequently, the total number of risk factors was lower in the SCAD group than in the no-SCAD group (SCAD, 0.8 ± 0.9 vs. no-SCAD, 1.9 ± 1.1, p < 0.001). The rate of patients underwent PCI was lower in the SCAD group than in the no-SCAD group (SCAD, 60% vs. no-SCAD 96%, p < 0.001). The PCI success rate was similar in the 2 groups (SCAD, 92.3% vs. no-SCAD, 94.1%, p = 1.000). Peak CK levels were significantly lower in the SCAD group (SCAD, 1689 ± 1536 vs. no-SCAD, 2,874 ± 2,854 U/L, p = 0.025).

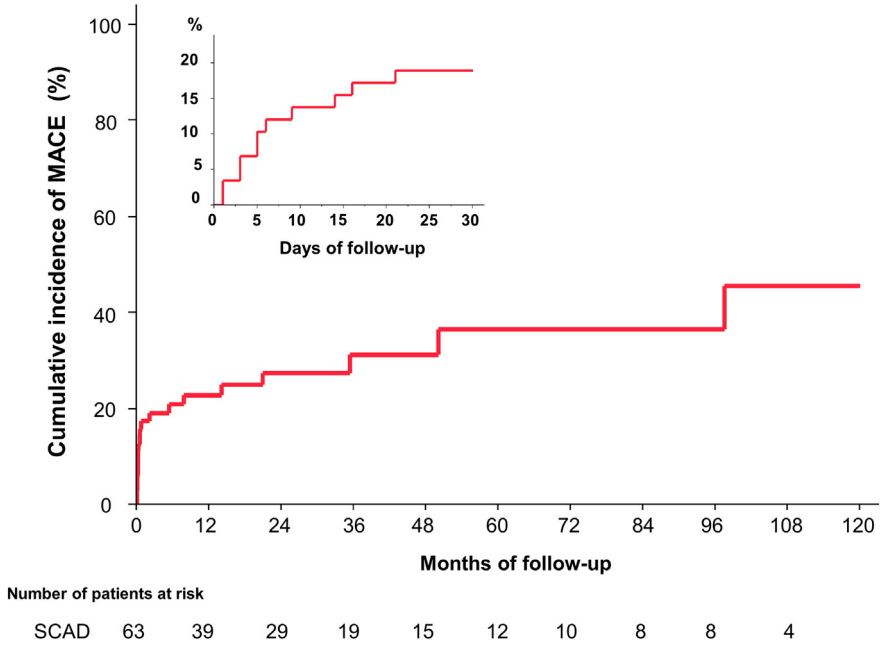

Fig. 2. Kaplan–Meier curves for MACE in the entire cohort. Kaplan–Meier curves show the 5-year rate of MACE. All patients with non-fatal AMI had recurrent SCAD. The 30-day and 5-year rates of MACE were 17% and 37%, respectively. MACE, major adverse cardiac events; other abbreviations as in Fig. 1.

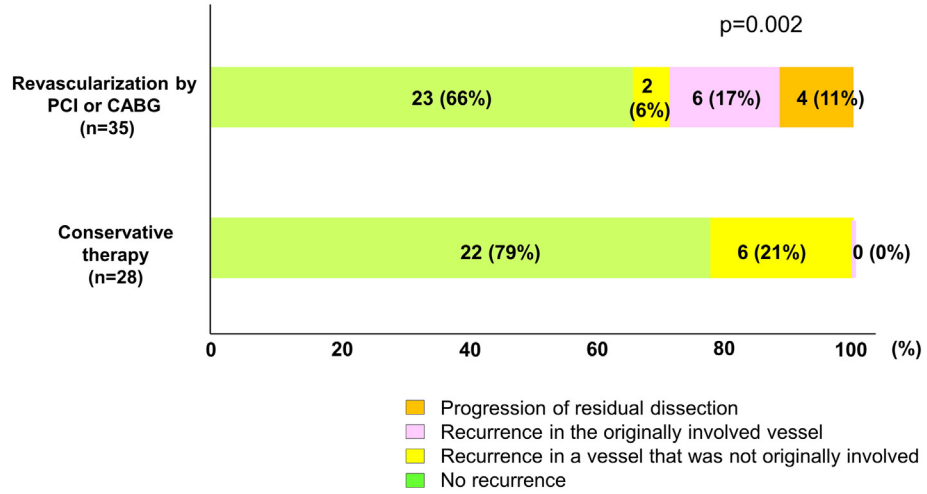

Fig. 3. Comparisons of the SCAD recurrence rate in coronary vessels with versus without coronary revascularization. Six of 35 patients (29%) in the revascularization group developed recurrence of SCAD in the originally involved vessel, whereas none of 28 patients in the conservative therapy group developed recurrence of SCAD in the originally involved vessel ($p = 0.002$). On the other hand, in the conservative therapy group, 21% (6 of 28 patients) of SCAD recurrences occurred in an originally uninvolved vessel, whereas 6% (2 of 35 patients) developed in an originally uninvolved vessel in the revascularization group. Abbreviation as in Fig. 1.

3.4.2. Long-term outcomes

Table 4 summarizes the occurrence of MACE during follow-up. During a median follow-up of 50 months (range, 1 to 197 months) with no loss to follow-up (n = 45) in the SCAD group, 17 (38%) patients developed the composite endpoint of MACE: 1 (2%) patient experienced sudden cardiac death and 16 (36%) experienced non-fatal AMI. Of note, among the 16 patients with non-fatal AMI, 4 had potential progression of primary SCAD and 12 had recurrent SCAD. Kaplan–Meier analysis

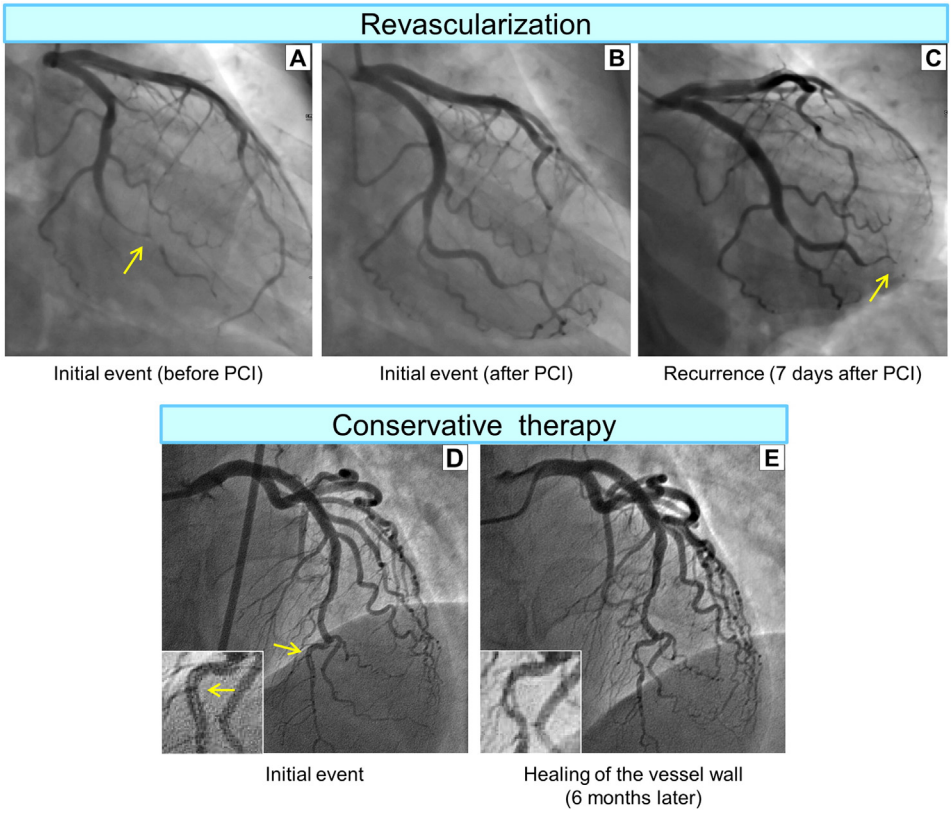

Fig. 4. Representative SCAD cases in the revascularization and conservative therapy groups. In a 37-year-old woman, subtotal occlusion due to SCAD (yellow arrow) was found in the distal left circumflex artery (A), which was re-perfused with percutaneous coronary intervention (PCI) (B). However, 7 days after PCI, recurrent SCAD (yellow arrow) developed in the originally involved vessel (C). In a 60-year-old woman, SCAD was found in the distal left anterior descending artery (yellow arrow) with TIMI 3 flow (D). Six months after conservative medical treatment, the vessel injury had spontaneously healed (E). TIMI, thrombolysis in myocardial infarction; other abbreviation as in Fig. 1.

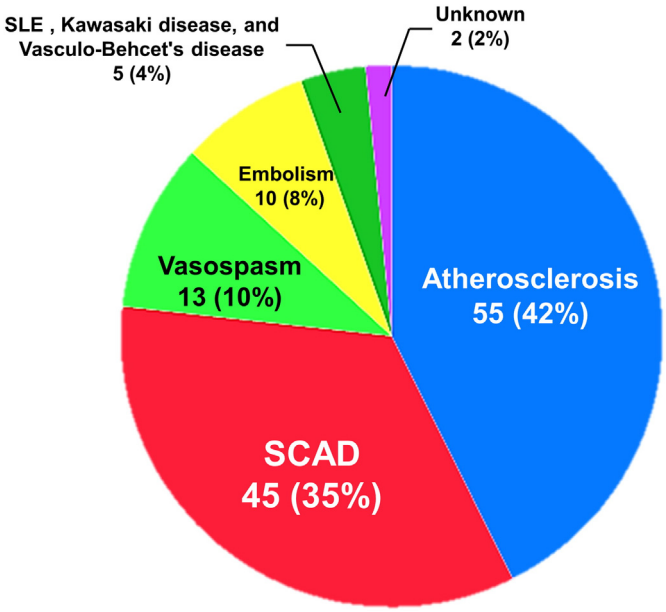

Fig. 5. Causes of AMI in females aged 50 years or younger. In 130 young female AMI patients, atherosclerosis was the most frequent cause of AMI. SCAD was the second. SLE, systemic lupus erythematosus; other abbreviations as in Fig. 1.

showed a significantly higher incidence of MACE (hazard ratio [HR], 6.92; 95% confidence interval [CI], 2.5 to 24.3; $p < 0.001$) in the SCAD group compared with the no-SCAD group (Fig. 6A).The 5-year rate of MACE in the SCAD group was significantly higher than that in the no-SCAD group (44% vs. 6%, $p < 0.001$). Moreover, the rate of SCAD recurrence was 27% and 42% of those occurred during the first 30 days (the median time to a second episode of SCAD was 113 days). On the other hand, there were no significant differences in the rate of cardiac death between the 2 groups ($p = 0.750$) (Fig. 6B).

4. Discussion

The major findings of this study are: 1) while the prevalence of SCAD was 0.31% in the AMI patients overall (n = 20,195), it was 35% in the subset of 130 young female AMI patients; 2) emotional stress was the most frequent precipitating factor; 3) 17% of the revascularization group developed recurrent SCAD in the originally involved PCI-treated vessel compared to none of the patients in the conservative therapy group; and 4) SCAD in young female AMI patients was associated a 7-fold higher rate of MACE than atherosclerosis as the etiology for AMI (44% vs. 6%, $p < 0.001$). To the best of our knowledge, this is the first multicenter study mechanistically evaluating the prevalence, clinical features, and long-term outcomes of SCAD focusing on young female patients with AMI.

Table 3
Baseline characteristics of SCAD and no-SCAD groups in young female AMI.

	SCAD group n = 45	no-SCAD group n = 55	p-Value
Age, yrs	41 ± 7	45 ± 6	0.002
BMI, kg/m^2	22.5 ± 4.6	25.0 ± 5.1	0.02
No of coronary risk factor	0.8 ± 0.9	1.9 ± 1.1	<0.001
Family history	4 (9)	3 (9)	1.00
Current smoking	18 (40)	23 (42)	1.00
Hypertension	10 (22)	33 (60)	<0.001
Diabetes mellitus	0	14 (25)	<0.001
Hyperlipidemia	6 (13)	30 (55)	<0.001
Lipid profile			
Total-cholesterol, mg/dl	170 ± 30	215 ± 51	<0.001
LDL-cholesterol, mg/dl	91 ± 25	134 ± 40	<0.001
Triglyceride, mg/dl	103 ± 78	162 ± 133	0.020
HDL-cholesterol, mg/dl	57 ± 18	49 ± 17	0.024
Anterior AMI	30 (67)	27 (50)	0.093
STEMI	39 (87)	51 (93)	0.339
Peak CK levels, IU/L	1689 ± 1536	2874 ± 2854	0.025
Revascularization	27 (60)	51 (93)	<0.001
30-day mortality	0	1 (2)	0.408

Values are n (%) or mean ± SD.
AMI indicates acute coronary myocardial infarction; CK, creatine kinase; HDL, high density lipoprotein; LDL, low density lipoprotein; STEMI, ST-elevation myocardial infarction.

Table 4
Summary of MACE during the follow-up period in young female AMI due to SCAD or no-SCAD group.

	SCAD group n = 45	No-SCAD group n = 55	p-Value
Composite endpoint, n (%)	17 (38)	4 (8)	<0.0001
Cardiac death, n (%)	1 (2)	1 (2)	1.00
Non-fatal acute myocardial infarction, n (%)	16 (36)	2 (4)	<0.0001
Progression of residual SCAD	4		
Recurrence of SCAD	12		
Urgent revascularization, n (%)	0	1 (2)	1.00

Categorical variables are expressed as n (%).
MACE, major adverse cardiac events (cardiac death, non-fatal acute myocardial infarction, urgent revascularization, fatal arrhythmia, or hospitalization for heart failure); SCAD, spontaneous coronary artery dissection.

4.1. Incidence and precipitating factors of SCAD

In this study, we showed that the prevalence of SCAD was 0.31% among AMI patients (Fig. 1, Study 1). Based on the multicenter Western Denmark Heart Registry [2], the incidence of SCAD in patients with acute coronary syndrome (0.2%) was similar to that in our cohort. When focusing on young female AMI patients aged 50 years or younger, the prevalence of SCAD in this study (35%) was higher than that of previous studies (8.7% to 24.2%) [6,16]. One possible explanation for differences between our present study and previous studies may be ethnic differences between Japanese and Western populations. It has been noted that SCAD is associated with specific clinical situations, including the peripartum and perimenopausal periods [17,18], use of contraceptives, and vigorous isometric exercise [19]. In the present study, the most frequent precipitating factor for SCAD was emotional stress (Table 1). However, extreme physical activity and the peripartum period were observed in 10% and 8% of patients, respectively. Saw et al. [20]. reported that intense emotional stress was a precipitating factor for SCAD in 26% of patients, compared to 4% for vigorous isometric exercise before AMI. These findings are consistent with the present results. Mental stress or vulnerability to mental crisis may be potential triggers for SCAD.

An association between FMD and SCAD [3,20,21] has been previously reported. One study of 50 patients with SCAD showed that 86% of patients with SCAD had FMD in at least one non-coronary territory [20]. FMD was less clearly understood as a potential precipitating factor of SCAD during the study period (after 2000) and we did not perform sufficient screening test. In the present study with incomplete screening, the prevalence of FMD was 20%.

4.2. Initial management of SCAD and vascular response

In a large recent single-center study, 43 of 87 patients (49%) at the Mayo Clinic underwent PCI with an overall PCI technical success rate of 65% (28 of 43 patients). In addition, unexpected disease propagation related to the PCI procedure (e.g., additional stenting for a developing dissection) occurred in 7 of 28 (25%) patients [3]. In the present study, revascularization with PCI and/or CABG was performed in 35 (56%) patients and the PCI technical success rate was 91% (Table 2). Despite a

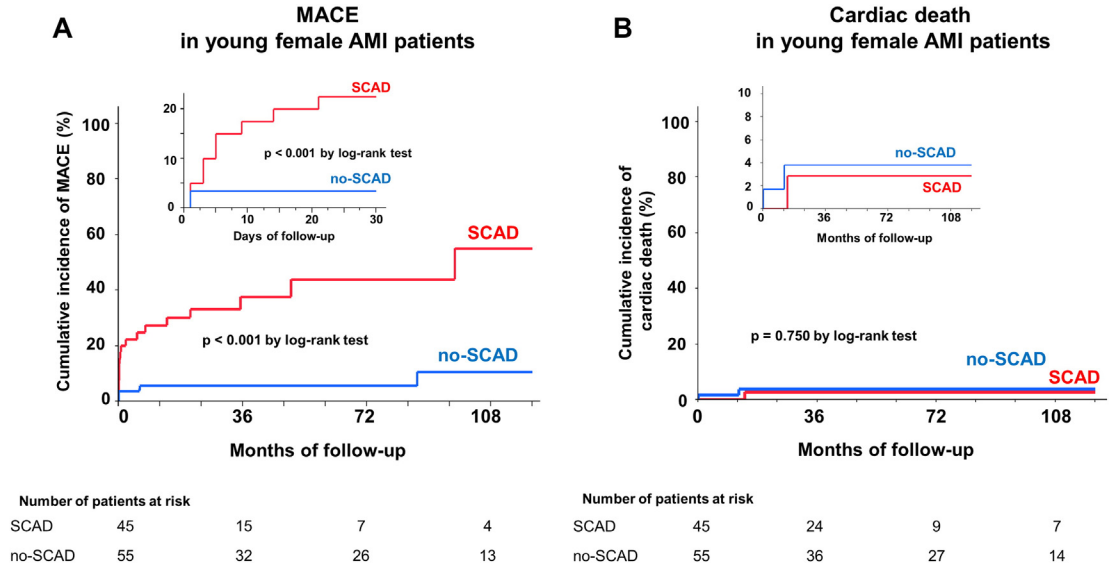

Fig. 6. Long-term outcomes in young female AMI patients in the SCAD and no-SCAD (atherosclerosis) groups. Kaplan–Meier curves show the 5-year rate of MACE (A) and all-cause death (B). With respect to MACE (A), the SCAD group (red line) had significantly poorer long-term outcomes than the no-SCAD group (blue line). In the SCAD group, all patients with non-fatal AMI developed potential progression of primary SCAD or recurrence of SCAD. On the other hand, Kaplan–Meier analysis of all-cause death (B) demonstrated comparable outcomes between the 2 groups. Abbreviation as in Figs. 1 and 2.

relatively high initial revascularization success rate, the rate of SCAD recurrence was comparable between the revascularization and conservative therapy groups. Importantly, in the revascularization group many cases of recurrent SCAD (17%) occurred in the originally involved vessel, whereas no cases of SCAD recurrence developed in the originally involved vessel in the conservative therapy group (Fig. 3). In addition, 68% of SCAD patients in the conservative therapy group experienced vessel wall healing during follow-up. These findings suggest that coronary interventional procedures might themselves delay arterial wall healing or be harmful to injured vessels. Based on our findings and those from previous studies [3,5,22], a conservative management strategy, except in patients undergoing revascularization for ongoing ischemia in a relatively extensive vascular territory, may be associated with a lower rate of SCAD recurrence.

4.3. Long-term outcomes of SCAD and the clinical impact of SCAD on young female patients with AMI

The recurrence rate for SCAD is considered low and patients with SCAD who survive the acute phase are thought to have a good long-term prognosis [5,6,23]. However, Tweet et al. [3]. recently reported that the rate of SCAD recurrence in their cohort of 87 patients was 17%, which was similar to the recurrence rate with AMI due to atherosclerosis. In addition, Saw et al. [4]. reported a high rate of SCAD recurrence (13%) in their cohort. Consistent with these recent studies, our study also demonstrated that the rate of SCAD recurrence among all study patients was unexpectedly higher (22%) than the rate reported in previous studies [5,6,23].

Regarding young female AMI patients, Gupta et al. [24]. reported an absence of significant declines in hospitalization rates over the past 10 years. Moreover, Dreyer et al. [25] reported that younger females have a higher risk for readmission after AMI compared to age-matched males, although younger females have a lower rate of hospitalization for AMI than younger males. These findings indicate that younger female patients with AMI have a phenotype that is distinct from those with atherosclerosis as the cause. In the present study, we analyzed the long-term outcomes of SCAD focusing on young female patients with AMI, that is, the population susceptible to SCAD. Our study demonstrated that the incidence of MACE in young female patients with SCAD was 7-fold higher than in patients with AMI due to atherosclerosis (44% vs. 6%, $p < 0.001$). Recurrent AMI due to recurrence of SCAD was the most frequent cardiac event in young female patients with SCAD. The high rate of SCAD recurrence (27%) in young female patients, along with relatively a high initial revascularization success rate (92%) observed here, indicates that PCI might not prevent future SCAD. Moreover, among these young female AMI patients with SCAD, 42% of recurrent SCAD occurred during the first 30 days and the median time to the second episode was 113 days. This finding highlights the need for close follow-up in young female patients with SCAD. Since the pathophysiology of SCAD in young female patients remains poorly understood, further research is needed to understand why it occurs and to identify effective prevention and treatment strategies.

4.4. Limitations

The present study has several limitations. First, this is a retrospective analysis and therefore is subject to the inherent weaknesses of such an analysis. Second, although to the best of our knowledge, this is the largest multicenter registry of SCAD focusing on young females, the sample size remains insufficient for statistical analysis. The prevalence of SCAD in our multicenter cohort was lower than those of recent single center cohorts [3,4]. One possible explanation for this discrepancy may be ethnic differences between Japanese and Western populations. Thirdly, since therapeutic strategy was not randomized, selection bias may limit the ability to compare outcomes according to the treatment. Regarding SCAD recurrence, we could not completely rule out the possibility of the propagation of residual SCAD. In addition, further studies are needed to determine the precise mechanism underlying a higher frequency of SCAD recurrence in a vessel that was not originally involved among patients who received conservative therapy. Finally, since we did not perform IVUS or OCT on all study patients to evaluate for atherosclerosis, some patients with both SCAD and CAD may have been included.

5. Conclusions

This multicenter study demonstrated that young female patients with SCAD represent a high-risk subgroup of patients with AMI and therefore need close follow-up.

Conflicts of interest

There are no relationships with industry.

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Appendix A. Angina pectoris–myocardial infarction multicenter investigations in Japan

National Cerebral and Cardiovascular Center (T. Nakashima, T. Doi, M. Fujino, T. Kanaya, Y. Tahara, T. Noguchi, S. Yasuda), Fukuyama Cardiovascular Hospital (K. Sato, S. Haruta), Saiseikai Fukuoka General Hospital (K. Osaka, K. Takesue, T. Serikawa, Y. Yamamoto), Kumamoto Chuo Hospital (S. Oshima), Saiseikai Kumamoto Hospital (H. Suzuyama, K. Nakao), Hyogo Brain and Heart Center (Y. Taniguchi), Tokyo Women's Medical University (H. Arashi, J. Yamaguchi), Sapporo Medical University (N. Kokubu, K. Tsuchihashi), Sakakibara Heart Institute (A. Seki, T. Toubaru), Sendai Heart Center (S. Fujii, T. Uchida), Nakada Internal Medicine Clinic (N. Omura), Dokkyo Medical University (M. Kikuchi), Yokohama City University Medical Center (K. Hashiba, K. Kimura), Kumamoto University Hospital (K. Tsujita, H. Ogawa), Kinki University Faculty of Medicine (S. Miyazaki), Shinkoga Hospital (T. Kawasaki), Chiba University Hospital (Y. Kobayashi), Hiroshima University Hospital (S. Kurisu), Iwate Medical University (T. Ito), Kyoto University (K. Ueshima), Kashiwara Municipal Hospital (K. Haze), Fukuoka Wajiro hospital (Y. Otsuka), University of Occupational and Environmental Health (S. Sonoda), Teine Keijinkai Hospital (M. Hirokami).

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