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Spontaneous Coronary Artery Dissection

Clinical Outcomes and Risk of Recurrence

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ABSTRACT

BACKGROUND Spontaneous coronary artery dissection (SCAD) is underdiagnosed and an important cause of myocardial infarction (MI), especially in young women. Long-term cardiovascular outcomes, including recurrent SCAD, are inadequately reported.

OBJECTIVES This study sought to describe the acute and long-term cardiovascular outcomes and assess the predictors of recurrent SCAD.

METHODS Nonatherosclerotic SCAD patients were prospectively followed at Vancouver General Hospital systematically to ascertain baseline, predisposing and precipitating stressors, angiographic features, revascularization, use of medication, and in-hospital and long-term cardiovascular events. Clinical predictors for recurrent de novo SCAD were tested using univariate and multivariate Cox regression models.

RESULTS The authors prospectively followed 327 SCAD patients. Average age was 52.5 ± 9.6 years, and 90.5% were women (56.9% postmenopausal). All presented with MI; 25.7% had ST-segment elevation MI, 74.3% had non-ST-segment elevation MI, and 8.9% had ventricular tachycardia/ventricular fibrillation. Precipitating emotional stressors were reported in 48.3% and physical stressors in 28.1%. Fibromuscular dysplasia was present in 62.7%, connective tissue disorder in 4.9%, and systemic inflammatory disease in 11.9%. The majority (83.1%) were initially treated medically, with only 16.5% or 2.2% undergoing in-hospital percutaneous coronary intervention or coronary artery bypass graft surgery, respectively. The majority of SCAD patients were taking aspirin and beta-blocker therapy at discharge and at follow-up. Median hospital stay was 3.0 days, and the overall major adverse event rate was 7.3%. Median long-term follow-up was 3.1 years, and overall major adverse cardiac event rate was 19.9% (death rate: 1.2%; recurrent MI: 16.8%; stroke/transient ischemic attack: 1.2%; revascularization: 5.8%). Recurrent SCAD occurred in 10.4% of patients. In multivariate modeling, only hypertension increased (hazard ratio: 2.46; $p = 0.011$) and beta-blocker use diminished (hazard ratio: 0.36; $p = 0.004$) recurrent SCAD.

CONCLUSIONS In our large prospectively followed SCAD cohort, long-term cardiovascular events were common. Hypertension increased the risk of recurrent SCAD, whereas beta-blocker therapy appeared to be protective. (J Am Coll Cardiol 2017;70:1148–58) © 2017 by the American College of Cardiology Foundation.

Spontaneous coronary artery dissection (SCAD) is increasingly recognized as an important cause of myocardial infarction (MI), particularly in young women. It is defined as a spontaneous tear in the coronary arterial wall that is not traumatic or iatrogenic; contemporary usage of the term is confined to nonatherosclerotic causes (1). This condition has been underdiagnosed for decades, but with

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an increased clinical index of suspicion, greater use of coronary angiography and intracoronary imaging (i.e., optical coherence tomography and intravascular ultrasonography) (2–4) and better pattern recognition on angiography (5), diagnosis of SCAD has improved substantially. Indeed, approximately one-half of the ~1,500 published SCAD cases were reported in the past half-decade (6–16).

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Contemporary case series have expanded the scientific knowledge of SCAD considerably. It is now estimated that SCAD is the underlying cause of 1.7% to 4% of acute coronary syndromes (ACS) (14,17) and accounts for 0.5% of sudden cardiac deaths (18). Furthermore, in young women <60 years of age, SCAD accounts for 22% to 35% of ACS presentations (14,16,19). It has become increasingly apparent that multiple factors may predispose to an arteriopathy that can weaken the arterial wall and increase vulnerability for dissection (7,8,10). This vulnerability can be exacerbated by precipitating stressors (emotional or physical), triggering dissection. Usually, conservative management is preferred to revascularization, except for high-risk unstable patients, because percutaneous coronary intervention (PCI) at the time of SCAD is associated with high failure rates, and most SCAD lesions heal spontaneously.

Nevertheless, this condition remains insufficiently understood. There are limited prospective series to discern the natural history and long-term cardiovascular outcomes of SCAD. The ideal management strategy has yet to be determined. There are no published randomized trials to guide therapy; current management recommendations are based on expert opinions, mainly from retrospective, observational SCAD studies. It is unknown whether standard medical pharmacotherapy used for ACS has similar risk-reduction benefits in SCAD patients. In particular, recurrent de novo SCAD has been frequently reported following the index SCAD event in 12% to 27% of cases (depending on follow-up duration), accounting for the majority of recurrent MI in this population (1). However, the risks of recurrence and strategies to minimize recurrence are unclear.

We systematically accrued and followed patients prospectively in a registry of SCAD patients at Vancouver General Hospital (VGH) since our first reported case series in 2011 (6). Our center has become a high-volume referral center for British Columbia and out-of-province SCAD patients in Canada, with a regular outpatient SCAD clinic and a dedicated SCAD-cardiac rehabilitation program (20). Accordingly, we aimed to describe the acute and long-term cardiovascular outcomes and assess the predictors of recurrent SCAD.

METHODS

We included patients with nonatherosclerotic SCAD who were evaluated at VGH, a quaternary referral center for prospectively and retrospectively identified SCAD patients. Patients judged to have atherosclerosis as the cause of SCAD were excluded. Patients were prospectively followed at the VGH SCAD clinic, and they consented to enrollment in the NACAD (Non-Atherosclerotic Coronary Artery Disease) or Canadian SCAD registries for long-term follow-up and approved by the University of British Columbia institutional review board. Patients were followed annually at a minimum.

BASELINE CHARACTERISTICS. The clinical history and baseline characteristics were obtained from patient interviews, hospital records, and patient-completed questionnaires. Baseline cardiovascular risk factors, medication on presentation, hospital presentation, electrocardiographic changes, in-hospital events, and angiographic and noninvasive imaging characteristics were recorded. All patients were interviewed, and they completed detailed questionnaires on potential predisposing and precipitating stressors, gynecological history, clinical symptoms, and family history. Significant emotional stress and intense physical activities (aerobic or isometric) preceding the SCAD event were queried and recorded from interviews and questionnaires (Online Appendix). Emotional stress was defined as currently experiencing major stress prior to hospital admission and categorized as severity level ≥3 on a 4-point scale (mild, moderate, high, or severe). Presence of physical stress was defined as new or unusually intense physical activity within 1 week of hospitalization or intense isometric activity defined as lifting >50 pounds. Active and prior hormone therapy (e.g., birth-control pills, fertility treatment, estrogen, progesterone, beta-human chorionic gonadotropin, and testosterone) was recorded. Other potential precipitating stressors (e.g., intense retching, vomiting, straining with bowel movements, use of recreational drugs, and active pregnancy) were also recorded. Medications administered on discharge and at each follow-up examination were recorded, including at time of recurrent event during follow-up.

A combination of focused patient interviews, detailed questionnaires, and angiography or computed tomography angiography (CTA) was used to identify potentially relevant predisposing arteriopathies for SCAD. Pregnancy history (gravidity and

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CABG = coronary artery bypass graft

FMD = fibromuscular dysplasia

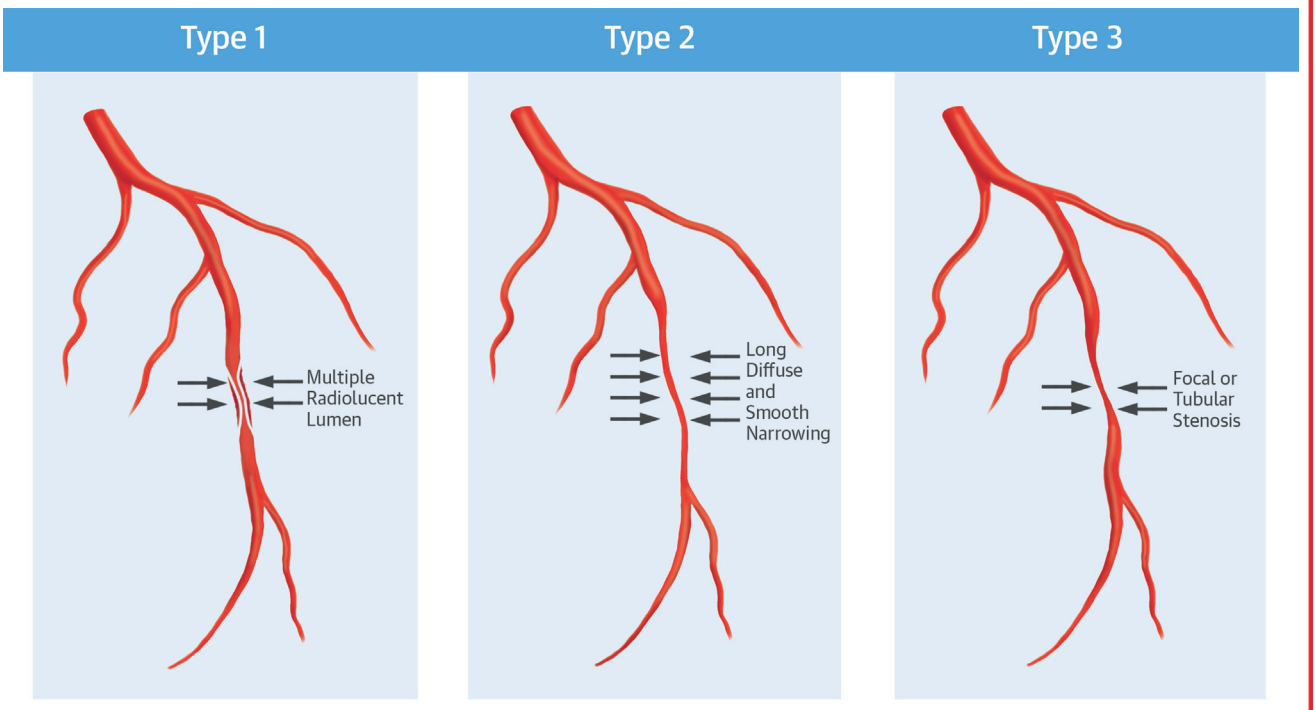
MACE = major adverse cardiac events

PCI = percutaneous coronary intervention

SCAD = spontaneous coronary artery dissection

VGH = Vancouver General Hospital

CENTRAL ILLUSTRATION **SCAD Classification**



Saw, J. et al. J Am Coll Cardiol. 2017;70(9):1148–58.

SCAD is classified angiographically into 3 types. Type 1 has the classic appearance of contrast dye staining of arterial wall with multiple radiolucent lumen. Type 2 shows long diffuse (typically >20 to 30 mm) and smooth narrowing that varies in severity. Type 3 has focal or tubular stenosis that mimics atherosclerosis, typically requiring intracoronary imaging to prove presence of intramural hematoma or double lumen. SCAD = spontaneous coronary artery dissection.

parity), presence of coexisting fibromuscular dysplasia (FMD), inherited connective tissue disorders (e.g., Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome type 4, and polycystic kidney disease), systemic inflammatory conditions (e.g., systemic lupus erythematosus, Crohn's disease, ulcerative colitis, rheumatoid arthritis, and celiac disease) predisposing to arteritis, and coronary artery spasm history were recorded. Postpartum SCAD was categorized as occurring early, within 6 weeks of delivery as defined by the World Health Organization (21), or late, up to 1 year after delivery (22). In this series, we classified multiparity as having given birth ≥4 times and grand multiparity ≥5 times with gestational age of ≥24 weeks; and grand multigravida as having been pregnant ≥5 times (10). Given our previous reports of SCAD's strong association with FMD (7,10), patients were routinely screened for extracoronary FMD in 3 arterial territories: renal, iliac, and cerebrovascular. Nonselective catheter-based angiographies with pigtail catheters of the renal and iliac arteries were preferred for patients with prospective SCAD diagnosis. Otherwise, CTA was performed for the renal and iliac arteries. CTA from the arch to circle of Willis was performed electively to assess for cerebrovascular FMD and intracranial aneurysm.

DIAGNOSIS AND OUTCOMES. All coronary angiograms were reviewed by 2 experienced cardiologists for SCAD, and classified according to our published angiographic SCAD classification (**Central Illustration**) (5). By definition, atherosclerotic, traumatic, or iatrogenic dissections were excluded from the diagnosis of SCAD. Type 1 angiographic SCAD appears as the classic contrast dye staining of arterial wall with multiple radiolucent lumen, with or without the presence of dye hang-up or slow contrast clearing from the lumen. Type 2 angiographic SCAD appears as diffuse (typically 20 to 30 mm) and smooth narrowing that can vary in severity. Type 3 angiographic SCAD mimics atherosclerosis with focal or tubular stenosis that typically requires optical coherence tomography

or intravascular ultrasonography to prove presence of intramural hematoma or double lumen (23). The coronary segment affected by SCAD was defined by the Bypass Angioplasty Revascularization Investigation classification (24). The number of dissected coronary arteries, location, stenosis severity, lesion length, and corresponding wall motion abnormality were recorded. Repeat coronary angiography could be performed at the discretion of the treating physicians. Results from repeat CTA or intracoronary imaging were recorded.

Diagnosis of FMD was made from invasive or noninvasive angiographic imaging based on the recent American Heart Association scientific statement on diagnostic definition of multifocal disease (string-of-beads appearance) (25). Nonselective catheter angiographies of the renal and iliac arteries were encouraged when patients were undergoing coronary angiography; otherwise, CTA or magnetic resonance angiography was performed. We required the presence of multifocal beading appearance in at least 1 extracoronary vasculature for a diagnosis of FMD in our cohort. Other changes deemed as possibly due to FMD, such as unifocal stenosis, pseudoaneurysm, aneurysm, dilation, and tortuosity were recorded as possible FMD but did not qualify for FMD diagnosis.

In-hospital events recorded included all-cause mortality, stroke, reinfarction (26), cardiogenic shock, congestive heart failure, severe ventricular arrhythmia (requiring defibrillation or antiarrhythmic agents), repeat revascularization (or unplanned revascularization), and cardiac transplantation, collectively termed in-hospital major adverse events. Extension of dissection of conservatively managed lesions was recorded. Long-term cardiovascular events included the composite of all-cause mortality, stroke, recurrent MI (including recurrent SCAD), congestive heart failure, and revascularization, collectively termed major adverse cardiac events (MACE). Recurrent SCAD was defined as de novo recurrent spontaneous dissection with new recurrent MI symptoms and enzyme elevation, which did not involve extension of dissection of the original SCAD lesion. Percutaneous coronary intervention outcomes were defined as follows: 1) successful angioplasty or stenting of the dissection with thrombolysis in myocardial infarction (TIMI) 3 flow and no residual dissection; 2) partially successful PCI was defined as angioplasty or stenting with residual dissection or stenosis of ≤50% of lumen diameter and with final TIMI 3 or improved flow; and 3) unsuccessful PCI was angioplasty or stenting with residual dissection or stenosis of >50% of lumen diameter or worsened TIMI flow compared to baseline or extension of dissection requiring "bail-out" coronary artery bypass graft (CABG). Spontaneous angiographic healing at follow-up angiography was defined as angiographic resolution of the coronary dissection with residual stenosis <50% and no further evidence of multiple lumen or contrast wall staining.

STATISTICAL ANALYSIS. Baseline characteristics of patients including demographics, cardiovascular risk factors, medical history, hospital presentation, coronary angiography details, predisposing arteriopathies, precipitating stressors, and extracoronary FMD were reported with descriptive statistics. Continuous variables were summarized as mean ± SD or median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. Post-discharge event rates were calculated based on person-time, which reports the number of new events divided by the sum of person-years at risk. Cox proportional hazards regression analyses were performed to identify univariate and multivariate clinical predictors of recurrent SCAD. Variables tested included cardiovascular risk factors, predisposing arteriopathies, precipitating stressors, medications used, and revascularization. Hazard ratios (HR) with corresponding 95% confidence intervals (CI) were reported. A 2-sided p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, New York).

RESULTS

We enrolled and prospectively followed 327 patients with nonatherosclerotic SCAD at VGH from April 2012 to December 2016. Baseline characteristics are summarized in **Table 1**. Mean age was 52.5 ± 9.6 years (**Figure 1**) (90.5% were ≤65 years of age), and the majority were women and Caucasian. A large proportion of women were postmenopausal. Most patients (69.7%) had 1 or no cardiovascular risk factors; however, baseline hypertension and dyslipidemia were present in 36.4% and 25.7% of participants, respectively. Migraines, depression, and anxiety were common. All patients presented with troponin-positive acute coronary syndrome (ACS), with one-quarter showing ST-elevation MI and the rest showing non-ST-elevation MI (**Table 2**). Ventricular tachycardia or fibrillation occurred in 8.9% (2.8% required cardioversion or an implantable cardioverter-defibrillator). The mean presenting left ventricular ejection fraction was 57.0%, and 85.6% of patients had wall motion abnormality.

Angiographic characteristics of the SCAD lesions are described in **Table 3**. Most cases of SCAD involved

TABLE 1 Baseline Characteristics

	Patients (N = 327)
Age, yrs	52.5 ± 9.6
Female	297 (90.8)
Body mass index, kg/m^2	24.4 (21.5-28.3)
Race	
Caucasian	268 (82.0)
East Asian	35 (10.7)
South Asian	17 (5.2)
African Canadian	3 (0.9)
First nation	2 (0.6)
Diabetes mellitus	15 (4.6)
Dyslipidemia	84 (25.7)
Hypertension	119 (36.4)
Current smoker	32 (9.8)
Family history of coronary artery disease	109 (33.3)
Previous MI	3 (0.9)
Cerebrovascular disease	13 (4.0)
Hypothyroidism	43 (13.1)
Postmenopausal	169* (56.9)
Migraines	119 (36.4)
Depression	74 (22.6)
Anxiety	44 (13.5)

Values are mean ± SD, n (%), or median (interquartile range). *n = 297.
MI = myocardial infarction.

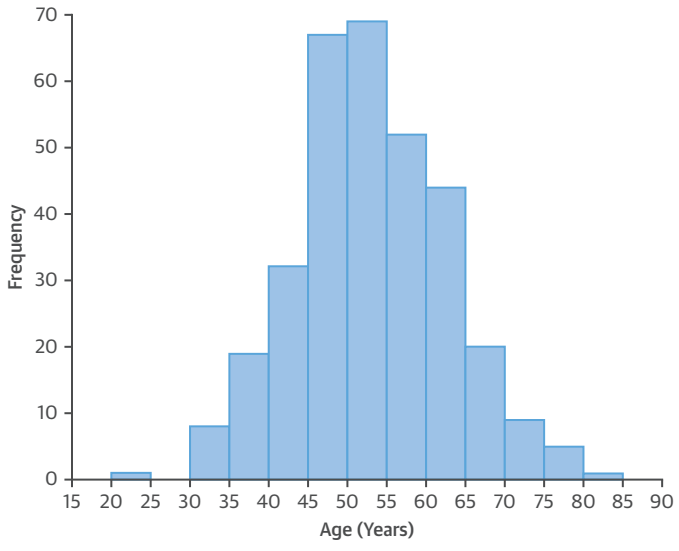
TABLE 2 Hospital Presentation

	Patients (N = 327)
Acute coronary syndrome	327 (100.0)
STEMI	84 (25.7)
NSTEMI	243 (74.3)
Normal ECG	63 (19.3)
Nonspecific ST-T changes	46 (14.1)
T inversions	80 (24.5)
ST depression	19 (5.8)
ST elevation <1 mm	22 (6.7)
VT/VF	29 (8.9)
Ejection fraction, %	57.0 (50.0-64.0)
Ejection fraction <50%	70 (21.8)
Left ventricular wall motion abnormality	
None	47 (14.4)
Hypokinesis	191 (58.4)
Akinesis	68 (20.8)
Dyskinesis	17 (5.2)
Precipitating factors	
Emotional stress	158 (48.3)
Physical stress	92 (28.1)
Heavy isometric activities	39 (11.9)

Values are n (%) or mean (interquartile range).
ECG = electrocardiogram; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.

a single coronary artery. Of the remainder, 65.2% had involvement of noncontiguous arteries and 34.8% of contiguous arteries. The most common coronary artery territory dissected was the left anterior descending artery, followed by the circumflex artery and the right coronary artery. The frequencies of coronary segments involved are shown in Figure 2. Among the 387 dissected arteries, more than two-thirds had type 2 angiographic SCAD, one-quarter had type 1, and 4.7% had type 3. The mean angiographic stenosis was 78.4 ± 18.7%, and mean dissection length was 42.7 ± 21.3 mm.

FIGURE 1 Age Distribution



In patients presenting with spontaneous coronary artery dissection, the mean age was 52.5 ± 9.6 years; 90.5% were 65 years of age and younger.

Precipitating stressors and predisposing arteriopathies were frequently reported and observed (Tables 2 and 4). Overall, 62.1% of patients reported potential precipitating stressors. Emotional stressors were reported in 48.3% and physical stressors in 28.1% preceding the SCAD event. Most patients (80.7%) underwent screening for cerebrovascular, renal, and iliac FMD with CTA or catheter angiography. Fibromuscular dysplasia was the most common potential predisposing arteriopathy (Table 5). Intracranial aneurysm was present in 14.1% of patients with FMD. Of note, 19.3% of patients were incompletely screened for FMD. Of the screening tests, catheter angiographies were performed for the renal arteries in 76.1% (216 of 284 screened cases), the iliac arteries in 74.0% (196 of 265 screened cases), and the cerebrovascular arteries in only 2.4% (6 of 254 screened cases). Other predisposing arteriopathies were observed much less frequently (Table 4), and there were 27.8% of cases deemed

TABLE 3 Coronary Artery Angiographic Characteristics

	Patients (N = 327)
SCAD involving >1 coronary artery	46 (14.1)
Noncontiguous >1 artery involved	30 (9.2)
Coronary artery territory involved	387 dissections
Left main artery	2 (0.6)
Left anterior descending artery	175 (45.2)
Circumflex artery	123 (31.8)
Right coronary artery	89 (23.0)
SCAD lesion characteristics	387 dissections
Type 1 angiographic SCAD	99 (25.6)
Type 2 angiographic SCAD	270 (69.8)
Type 3 angiographic SCAD	18 (4.7)
Angiographic stenosis severity, %	78.4 ± 18.7
QCA dissection length, mm	42.7 ± 21.3
TIMI flow	
TIMI 0	51 (13.2)
TIMI 1	31 (8.0)
TIMI 2	46 (11.9)
TIMI 3	259 (66.9)

Values are n (%) or mean ± SD, unless otherwise indicated.
QCA = quantitative coronary angiography; SCAD = spontaneous coronary artery dissection; TIMI = Thrombolysis In Myocardial Infarction.

idiopathic without underlying potential predisposing arteriopathy.

The median hospital stay was 3.0 days (IQR: 2.0 to 5.0 days). Most patients (83.2%) were treated conservatively as their initial treatment strategy; of these, 9 of 272 patients (3.3%) had extension of dissection and required subsequent in-hospital revascularization (2.2% PCI; 1.1% CABG). Overall, 61 patients (18.7%) underwent revascularization, including 16.5% who had PCI and 2.1% who had CABG. Eight patients underwent fibrinolysis, of whom 4 required subsequent revascularization. Percutaneous coronary intervention was deemed successful in 43.1% of cases, partially successful in 25.9%, and unsuccessful in 31.0%. Overall, the in-hospital major adverse event rate was 7.3%, with in-hospital mortality 0%, stroke 1.5%, recurrent MI 4.6%, and urgent unplanned revascularization 4.3% (Table 6).

Post-discharge, the median long-term duration of follow-up was 3.1 years (IQR: 1.49 to 5.49) with an overall MACE rate of 19.9% (including mortality 1.2%, recurrent MI 16.8%, recurrent SCAD 10.4%, stroke or transient ischemic attack 1.2%, revascularization 5.8%). The overall MACE rate was 5.8 events/100 person-years (Table 6), with MI as the most frequently occurring long-term event.

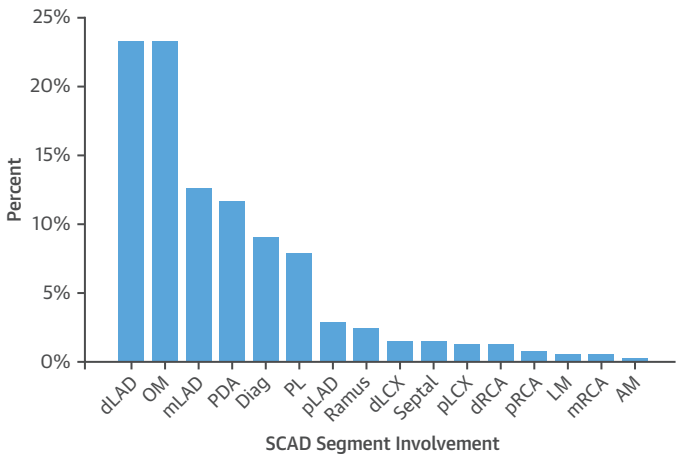
The medications at hospital discharge and last clinical follow-up are listed in Table 7. More than 9 of 10 patients were discharged home on aspirin therapy and a significant proportion on clopidogrel or a beta-blocker. At last clinical follow-up, the percentage of patients remaining on aspirin and a beta-blocker was high. In addition, 55 of 74 patients (74.3%) with depression were taking an antidepressant, and 25 of 44 patients (56.8%) with anxiety were taking anti-anxiety medication.

Recurrent de novo SCAD occurred in 34 patients (10.4%). Of these, 8 patients (23.5%) were not taking any medication when they presented with their recurrent event (either subsequently stopped or not prescribed any medication post-SCAD). From Cox regression analysis, significant univariate predictors of recurrent SCAD were hypertension and use of a beta-blocker, a calcium-channel blocker, or aspirin individually (Table 8). However, in multivariate analysis, only use of hypertension and beta-blocker remained significantly independent predictors of recurrent SCAD, with hypertension associated with increased risk of recurrent SCAD and beta-blocker use with reduced risk. Kaplan-Meier event-free survival curves are shown in Figures 3 and 4.

DISCUSSION

In this largest reported cohort of prospectively followed patients from our SCAD registries, we comprehensively assessed acute and long-term

FIGURE 2 Frequency of Coronary Artery Segment Dissection



The dLAD and OM were dissected almost twice as often as other segments. AM = acute marginal; Diag = diagonal; dLCX = distal left circumflex; dLAD = distal left anterior descending artery; dRCA = distal right coronary artery; LM = left main; mLAD = mid left anterior descending artery; mRCA = mid right coronary artery; OM = obtuse marginal; PDA = posterior descending artery; PL = posterolateral; pLAD = proximal left anterior descending artery; pLCX = proximal left circumflex; pRCA = proximal right coronary artery; SCAD = spontaneous coronary artery dissection.

TABLE 4 Potential Predisposing Factors

	Patients (N = 327)
FMD	205 (62.7)
Systemic inflammatory condition	39 (11.9)
Connective tissue disorder	16 (4.9)
On hormonal therapy	38 (11.6)
Postpartum	7* (2.4)
Multiparous (≥4 births)	25* (8.8)
Grand multiparity (≥5 births)	7* (2.4)
Grand multigravida (≥5 pregnancies)	39* (11.9)
Idiopathic	91 (27.8)

Values are n (%). *n = 297.
FMD = fibromuscular dysplasia.

cardiovascular outcomes and explored clinical predictors of recurrent events in 327 patients, including potential benefits of administering specific medications. Importantly, despite a predominantly conservative initial treatment strategy in 83.1% of patients, in-hospital adverse events were low, with a recurrent MI rate of 4.6%, need for unplanned revascularization rate of 4.3%, and 100% early survival to discharge. However, long-term adverse events were common at a median follow-up of 3.1 years, with a recurrent MI event rate of 16.8%, primarily due to recurrent SCAD in 10.4% of patients. In Cox regression multivariate analysis, the presence of hypertension was associated with increased risk of recurrent SCAD (HR: 2.46), and beta-blocker use was associated with reduced risk of recurrent SCAD (HR: 0.36).

One key finding of our study is a list of significant clinical predictors of recurrent SCAD, which has not been previously reported in other SCAD series. Recurrent SCAD is an important complication in SCAD patients, accounting for the majority of recurrent MI at long-term follow-up that is unrelated to PCI.

TABLE 5 Involvement With Noncoronary FMD

	Patients
Prevalence of FMD	327
FMD diagnosed	205 (62.7)
FMD not diagnosed	122 (37.3)
FMD possible	17 (5.2)
Incomplete screening	63 (19.3)
Screened cerebrovascular, renal, iliac	42 (12.8)
FMD vascular involvement	205
Renal arteries	139 (67.8)
Iliac arteries	114 (55.6)
Cerebrovasculature	100 (48.8)
Cerebral aneurysm	29 (14.1)

Values are n or n (%).
FMD = fibromuscular dysplasia.

TABLE 6 In-Hospital and Follow-Up MACE

	Patients (N = 327)
In-hospital events	
Death	0 (0.0)
MI	15 (4.6)
Stroke/TIA	5 (1.5)
Unplanned revascularization	14 (4.3)
Cardioversion or ICD	9 (2.8)
Overall major adverse events	24 (7.3)
Long-term events	
Death	0.3
MI	4.8
Recurrent de novo SCAD	2.8
Stroke/TIA	0.3
Revascularization	1.5
Overall MACE	5.8
Angina hospitalization	2.0

Values are n (%) or %/yr.
ICD = implantable cardioverter-defibrillator; MACE = major adverse cardiac events; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 3.

Recurrent SCAD has been reported in up to 30% of cases with a 4- to 10-year follow-up in different series (8,10,11,16). However, the definition of recurrent SCAD in these series included both patients with extension of dissection of the index SCAD lesion and those with subsequent de novo SCAD. Previous reports had differentiated between the angiographic involvement and timing of presentation of these disparate forms of "recurrent SCAD" (11,27). Extension of dissection involved expansion of the intramural hematoma at either edge, usually occurring early (within 30 days) from the index SCAD event (27). In contrast, de novo SCAD in a segment not previously dissected occurred beyond 30 days of the index SCAD event (27). For the purpose of this study, we included only the latter form (recurrent de novo SCAD) in our analysis of recurrent SCAD, because this

TABLE 7 Medications at Discharge and Last Follow-Up

	Medications at Discharge (N = 288)*	Medications at Last Follow-Up (N = 327)
Aspirin	265 (92.0)	288 (88.1)
Clopidogrel (or other ADP antagonist)	179 (62.2)	83 (25.4)
Beta-blocker	239 (83.0)	263 (80.4)
Calcium-channel blocker	48 (16.7)	48 (14.7)
Statin	156 (54.2)	120 (36.7)
ACE inhibitor/ARB	166 (57.6)	161 (49.2)
Nitroglycerin	60 (20.8)	42 (12.8)

Values are n (%). *Incomplete data for 39 patients at discharge.
ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate; ARB = angiotensin-receptor blocker.

represents a new dissection anatomically independent of the index SCAD event.

With this specific definition of recurrent SCAD, we evaluated the clinical predictors of recurrent SCAD, incorporating relevant variables including baseline characteristics, predisposing arteriopathies (e.g., FMD, connective tissue disorder, systemic inflammatory disease), precipitating stressors, medications used, and revascularization. In multivariate Cox regression analysis, hypertension increased the risk of recurrent SCAD by more than 2-fold (HR: 2.46; p = 0.011), whereas beta-blocker use lowered recurrent SCAD risk by almost two-thirds (HR: 0.36; p = 0.004). These findings have important implications for patient management, namely that beta-blocker therapy appeared to be protective in reducing risk of recurrent SCAD. Beta-blockers reduce arterial shear stress by reducing myocardial contractility, heart rate, and blood pressure and are essential in managing aortic dissection (28). The adoption of beta-blockade in the management of SCAD patients has a parallel with data from the aortic dissection studies, where it had been shown to reduce aneurysmal degeneration, dissection-related aortic procedures, and mortality (29). Our study was the first to show that beta-blocker therapy is beneficial in SCAD patients, reducing the risk of recurrent dissection compared to that in patients not taking beta-blockade. In SCAD patients, we theorized that reduction in myocardial contractility and blood pressure by beta-blockade reduced coronary arterial wall stress and therefore protected against coronary dissection, especially when patients experienced additional arterial stresses, such as catecholamine surges from emotional and physical stressors.

The other important finding was that an underlying history of hypertension predicted recurrent SCAD. Systemic hypertension increases circumferential arterial wall stress and induces arterial remodeling, including proliferation of vascular smooth muscle cells and breakdown of medial elastin, thus increasing risk of local fatigue and endothelial damage (30–32). These acute and chronic arterial changes can empirically increase risk of arterial dissection (33–35). Aggressive management of blood pressure is an essential component in the acute and long-term management of patients with aortic dissection (28). Among patients with SCAD, we theorized that systemic hypertension can similarly increase coronary arterial wall stress and render them more susceptible to recurrent SCAD. It would appear, therefore, that beta-blockers would be the preferred antihypertensive class in patients with SCAD and secondary agents should be considered to ensure achievement of optimal blood pressure goals, but that will require further study.

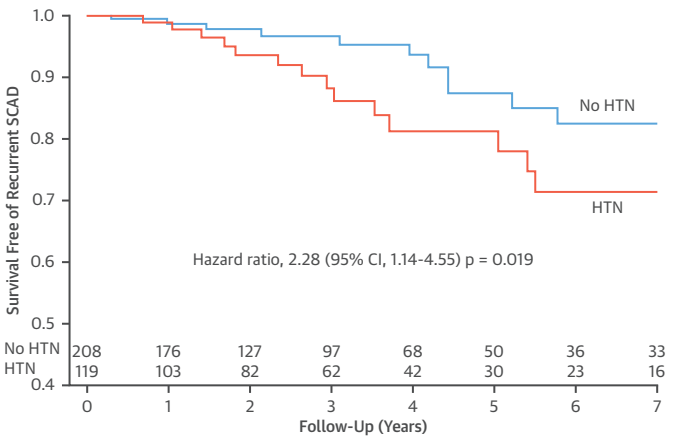
TABLE 8 Univariate and Multivariate Predictors of Recurrent SCAD

	Univariate Model		Multivariate Model	
Predictor	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Hypertension	2.28 (1.14–4.55)	0.019	2.46 (1.23–4.93)	0.011
Beta-blocker	0.39 (0.19–0.78)	0.008	0.36 (0.18–0.73)	0.004
Calcium-channel blocker	2.57 (1.25–5.31)	0.011		
Aspirin	0.36 (0.18–0.73)	0.004		

CI = confidence interval; SCAD = spontaneous coronary artery dissection.

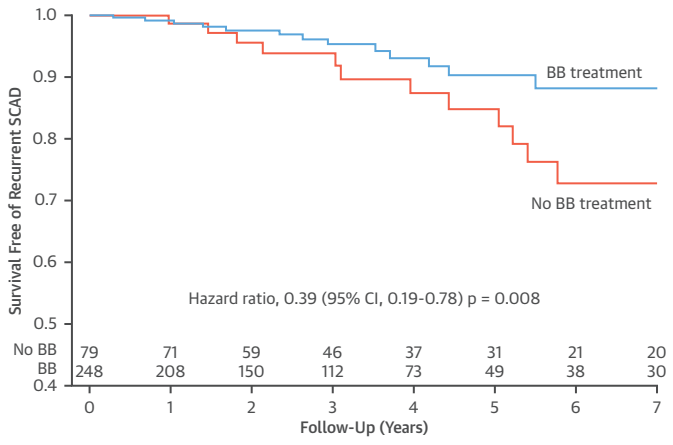
In the study by Eleid et al. (36), coronary tortuosity was evaluated as an angiographic predictor of recurrent SCAD in 246 patients. They found severe coronary tortuosity (defined as ≥2 consecutive curvatures ≥180°) had a borderline association with higher risk of recurrent SCAD (HR: 3.29; 95% CI: 0.99 to 8.29; p = 0.05). However, a high tortuosity score of >5 did not significantly predict higher risk of recurrent SCAD (p = 0.16). In that smaller series, clinical variables of age, sex, body mass index, hypertension, active tobacco use, peripartum status, and extracoronary vasculopathy did not predict recurrent SCAD. Interestingly, angiographic markers of tortuosity were associated with extracoronary vasculopathy, including FMD (p < 0.05), in this study. Our group also reported that coronary tortuosity was uniformly observed in patients with suspected coronary FMD (37). Thus, coronary tortuosity appears to

FIGURE 3 Survival Free of Recurrent SCAD: Hypertension



Presence of HTN increased the risk of recurrent SCAD. CI = confidence interval; HTN = hypertension; SCAD = spontaneous coronary artery dissection.

FIGURE 4 Survival Free of Recurrent SCAD: Beta-Blocker Treatment



BB treatment reduced the risk of recurrent SCAD. BB = beta-blocker; other abbreviations as in Figure 3.

be a marker of underlying coronary arteriopathy (e.g., due to FMD), as opposed to being the pathophysiological cause of dissection. In our series, coronary tortuosity was not assessed and FMD was not a predictor of recurrent SCAD.

The acute and long-term management of SCAD remains contentious as there have been no randomized controlled trials assessing optimal treatment strategy. Experts in the field endorse a conservative (nonrevascularization) treatment strategy for acute SCAD lesions without high-risk features, given the suboptimal acute PCI outcomes and the tendency for SCAD lesions to heal spontaneously (9–11). In our large SCAD registry, more than 80% of patients were treated conservatively as the initial strategy; the remainder underwent revascularization at the treating physician's discretion, but typically in the setting of ongoing or recurrent chest pain, ischemia, left main dissection, or ventricular arrhythmias. Only 3.3% of conservatively treated patients had subsequent extension of dissection and required unplanned revascularization in-hospital. Thus, the low in-hospital complication rate observed with primarily a conservative approach in our cohort supported the expert recommendations. Furthermore, the outcomes with PCI were somewhat disappointing, unsuccessful in 31.0% of cases and only partially successful in 25.9%. This highlighted the challenge with PCI of SCAD lesions and confirmed that PCI should be relegated to a second-line treatment strategy, except for high-risk anatomy or clinical instability.

In this expanded SCAD cohort, we confirmed prior observations that a large proportion of patients have underlying, potentially predisposing arteriopathies and precipitating stressors (7,8,10,11,38). We previously discovered a dominant association with FMD upon routine screening, with extracoronary FMD identified in 69% to 86% of our earlier SCAD cohorts depending on the modality and extent of screening (7,10); this association was confirmed by other series (11,38). In this current cohort of 327 patients, 62.7% had extracoronary FMD, although 19.3% had not undergone complete screening (screening coronary CTA or angiography of the renal, iliac, and cerebrovascular arteries). Other predisposing arteriopathies were less frequently observed, including postpartum SCAD (only 2.8% of cases). Overall, 27.8% of arteriopathies were deemed idiopathic. Although these arteriopathies are suspected to weaken the coronary arteries, making them more susceptible to dissections, there is no coronary histological proof to confirm a direct causal link.

Preceding precipitating stressors were reported in 62.1% of patients: emotional stressors in 48.3% and physical stressors in 28.1% (11.9% with heavy isometric exertion). These stressors can increase catecholamine surges and increase intrathoracoabdominal pressures that can increase arterial shear stress, which may explain the benefit of beta-blockers in reducing such stresses for recurrent SCAD. We routinely advise our patients to avoid intense isometric activities (limiting weight bearing to ~30 pounds) and competitive sports (e.g., marathon, triathlon), as well as to minimize emotional stress (offering psychosocial support if required), as incorporated in our dedicated SCAD cardiac rehabilitation protocol (20). However, there is no clinical trial evidence that limiting such triggers will reduce risk of recurrent SCAD. Nevertheless, we previously showed that our dedicated SCAD cardiac rehabilitation multidisciplinary program, which incorporated these recommendations, together with exercise rehabilitation, psychosocial counseling, education, and peer group support, improved our participants' long-term cardiovascular outcomes (20). It is unknown whether this benefit was derived from exercise rehabilitation, avoidance of triggers, or beta-blocker use (~85% of the 70-patient SCAD rehab cohort was receiving a beta-blocker drug).

The ideal pharmacotherapy for SCAD is undetermined given the lack of randomized data, and standard ACS medications may not be beneficial. Nonetheless as previously described, we routinely administer aspirin and beta-blockers long term and clopidogrel for 1 to 12 months following the acute SCAD event (1,2). An angiotensin-converting enzyme

inhibitor (or angiotensin-receptor blocker) is routinely administered only to patients with significant left ventricular dysfunction, and statins are given to patients with pre-existing dyslipidemia (8,39). At discharge, 92.0% of our study patients were receiving aspirin, 83.0% were receiving beta-blockers (mostly metoprolol or bisoprolol), and 62.2% were taking clopidogrel. At long-term follow-up, most patients remained taking aspirin and beta-blocker therapy (88.1% and 80.4%, respectively); 49.2% received an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and 36.7% were receiving statin therapy. Aside from beta-blockers, none of the other agents were shown to reduce the risk of recurrent SCAD in our study. The utility of these agents in SCAD patients should be further explored in other studies, such as the SAFER-SCAD (Statin and Angiotensin-converting Enzyme Inhibitor on Symptoms in Patients With SCAD) study (NCT02008786). Although randomized trials will provide more definitive evidence on SCAD pharmacotherapy, the low overall incidence of SCAD makes this endeavor very challenging. Thus, supportive evidence for medical management realistically is likely to be derived from observational registries in the foreseeable future.

STUDY LIMITATIONS. Although our study is the largest prospectively followed SCAD cohort reported to date, this remains a nonrandomized observational study. Acute in-hospital management of patients was carried out at the discretion of the treating physicians, and the rationale for revascularization was not routinely documented, although a conservative approach was generally favored. Although we attempted to screen for predisposing arteriopathies in all patients, there remained ~20% who were incompletely screened for FMD. Different imaging modalities were used for FMD screening in different vasculature, with CTA primarily used for cerebrovasculature (89.4% of cases), and a combination of catheter-angiography (~75%) or CTA (~23%) for renal/iliac arteries, which may explain the different incidence rates of FMD in different vascular trees. Furthermore, genetic studies and inflammatory markers for comprehensive evaluation of connective tissue disorders and systemic inflammatory diseases were not performed routinely. Thus, idiopathic forms of SCAD may be overestimated. Finally, the number of recurrent SCAD events was relatively small, and there might have been residual confounders that were not adequately adjusted for in our multivariable analysis.

CONCLUSIONS

In our large, prospectively followed SCAD cohort, a predominantly conservative treatment strategy was associated with low in-hospital adverse events. However, long-term cardiovascular events were common, especially recurrent MI due to recurrent SCAD. Hypertension was significantly associated with an increased risk of recurrent SCAD, whereas beta-blocker use was significantly associated with reduced risk of recurrent SCAD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Spontaneous coronary artery dissection is an important but under-recognized cause of MI, especially in young women with fibromuscular dysplasia.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: MI in patients with SCAD is often precipitated by physical or emotional stress. Given the relatively poor outcomes of PCI, conservative management is generally preferred. Hypertension is associated with a greater risk and treatment of beta-blocking drugs with a lower risk of recurrent SCAD.

TRANSLATIONAL OUTLOOK: Further studies are needed to discover the mechanisms responsible for initial and recurrent SCAD and to define optimum management strategies.

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KEY WORDS beta-blocker, coronary angiography, fibromuscular dysplasia, hypertension, myocardial infarction, women

APPENDIX For the interview questionnaire form, please see the online version of this article.