Spontaneous coronary artery dissection (SCAD) is considered a rare condition, but the true prevalence in the overall population is unknown. It has been reported to be an infrequent cause of acute coronary syndrome (0.1%–4%) and sudden cardiac death (0.4%). To date, <800 cases have been reported in the literature since the first autopsy report in 1931. This is a clear under-representation of this disease, mostly because of the challenges of conventional coronary angiography in diagnosing SCAD. In addition, there is disparate sex and age predisposition according to the cause of SCAD. SCAD is broadly classified into atherosclerotic and nonatherosclerotic (NA) causes, which affect dissimilar populations with different risks and angiographic characteristics. NA-SCAD is distinct in that younger women are affected, especially those without (or low incidence of) cardiovascular risk factors. In our review of young women aged ≤50 years undergoing coronary angiography, we found that SCAD was the cause of myocardial infarction (MI) in 24% of cases. Thus, in the select population of younger women presenting with MI, SCAD is not rare.

**Background**—Nonatherosclerotic spontaneous coronary artery dissection (NA-SCAD) is underdiagnosed and an important cause of myocardial infarction in young women. The frequency of predisposing and precipitating conditions and cardiovascular outcomes remains poorly described.

**Methods and Results**—Patients with NA-SCAD prospectively evaluated (retrospectively or prospectively identified) at Vancouver General Hospital were included. Angiographic SCAD diagnosis was confirmed by 2 experienced interventional cardiologists and categorized as type 1 (multiple lumen), 2 (diffuse stenosis), or 3 (mimic atherosclerosis). Fibromuscular dysplasia screening of renal, iliac, and cerebrovascular arteries were performed with angiography or computed tomographic angiography/MR angiography. Baseline, predisposing and precipitating conditions, angiographic, revascularization, in-hospital, and long-term events were recorded. We prospectively evaluated 168 patients with NA-SCAD. Average age was 52.1±9.2 years, 92.3% were women (62.3% postmenopausal). All presented with myocardial infarction. ECG showed ST-segment elevation in 26.1%, and 3.6% had ventricular tachycardia/ventricular fibrillation arrest. Fibromuscular dysplasia was diagnosed in 72.0%. Precipitating emotional or physical stress was reported in 56.5%. Majority had type 2 angiographic SCAD (67.0%), only 29.1% had type 1, and 3.9% had type 3. The majority (134/168) were initially treated conservatively. Overall, 6 of 168 patients had coronary artery bypass surgery and 33 of 168 had percutaneous coronary intervention in-hospital. Of those treated conservatively (n=134), 3 required revascularization for SCAD extension, and all 79 who had repeat angiogram ≥26 days later had spontaneous healing. Two-year major adverse cardiac events were 16.9% (retrospectively identified group) and 10.4% (prospectively identified group). Recurrent SCAD occurred in 13.1%.

**Conclusions**—Majority of patients with NA-SCAD had fibromuscular dysplasia and type 2 angiographic SCAD. Conservative therapy was associated with spontaneous healing. NA-SCAD survivors are at risk for recurrent cardiovascular events, including recurrent SCAD. (Circ Cardiovasc Interv. 2014;7:00-00.)

**Key Words:** coronary angiography • coronary artery dissection, spontaneous • fibromuscular dysplasia • myocardial infarction • women

Spontaneous coronary artery dissection (SCAD) is considered a rare condition, but the true prevalence in the overall population is unknown. It has been reported to be an infrequent cause of acute coronary syndrome (0.1%–4%) and sudden cardiac death (0.4%). To date, <800 cases have been reported in the literature since the first autopsy report in 1931. This is a clear under-representation of this disease, mostly because of the challenges of conventional coronary angiography in diagnosing SCAD. In addition, there is disparate sex and age predisposition according to the cause of SCAD. SCAD is broadly classified into atherosclerotic and nonatherosclerotic (NA) causes, which affect dissimilar populations with different risks and angiographic characteristics. NA-SCAD is distinct in that younger women are affected, especially those without (or low incidence of) cardiovascular risk factors. In our review of young women aged ≤50 years undergoing coronary angiography, we found that SCAD was the cause of myocardial infarction (MI) in 24% of cases. Thus, in the select population of younger women presenting with MI, SCAD is not rare.
WHAT IS KNOWN

- Spontaneous coronary artery dissection (SCAD) is considered a rare condition but is underdiagnosed.
- It was thought to affect predominantly younger women.
- We recently discovered a strong association between SCAD and fibromuscular dysplasia.

WHAT THE STUDY ADDS

- In this study, SCAD affected predominantly women (significant proportion were postmenopausal) and was commonly associated with predisposing arteriopathies (especially fibromuscular dysplasia) and precipitating stressors.
- The most common angiographic appearance was a diffuse long and smooth stenosis (type 2 angiographic SCAD).
- Conservative management of stable patients with SCAD was viable and associated with spontaneous angiographic healing.
- Recurrent cardiovascular events were frequent after the initial SCAD event.

Given the infrequency and poor recognition of this condition, there is limited literature on the cause and the natural history of SCAD. Several predisposing arteriopathies and precipitating stressors have been associated with NA-SCAD (Table 1), but the reported relative frequency of these factors varies widely and the majority of patients were labeled idiopathic in older literature. We recently discovered a strong association between SCAD and fibromuscular dysplasia (FMD), and subsequently confirmed that the majority of patients with SCAD in our initial 50 patient-cohort had noncoronary FMD with routine screening. This strongly implicates FMD as an important cause of SCAD because such a dominant and frequent association was observed, despite the rarity of both conditions. Nevertheless, a much larger cohort is required to confirm the prevalence of FMD and other predisposing arteriopathies and precipitating stressors and to correlate these causes to cardiovascular outcomes.

There also remains an immense knowledge gap for physicians managing this challenging condition, with a lack of consensus on patients with SCAD has not been adequately explored. The decision to proceed with percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) differs widely among clinicians and depends on the acute presentation. A conservative approach is typically recommended unless there is ongoing ischemia, recurrent chest pain, hemodynamic instability, or left main (LM) dissection. However, this recommended strategy is not based on randomized data, and the acute and long-term outcomes of a conservative or revascularization approach are unclear.

We prospectively evaluate patients with NA-SCAD at Vancouver General Hospital, a large quaternary referral center for SCAD follow-up in British Columbia. We sought to evaluate the prevalence of potential predisposing arteriopathies and precipitating stressors and cardiovascular outcomes with conservative and revascularization therapy.

Method

Study Population

Patients with NA-SCAD evaluated at Vancouver General Hospital constitute this study cohort. Our center is the quaternary referral center for prospectively and retrospectively identified patients with SCAD in the province of British Columbia. Patients judged to have atherosclerosis as the underlying condition causing SCAD were excluded for the purpose of this study. British Columbia patients with NA-SCAD represented the vast majority of our patient-cohort and are followed up prospectively at our SCAD clinic. Out-of-province patients (only 6) are contacted by telephone follow-up. Patients with NA-SCAD followed up prospectively at our SCAD clinic are consented for enrollment in our Non-Atherosclerotic Coronary Artery Disease registry for long-term annual follow-up, approved by the University of British Columbia Institutional Review Board.

Baseline Characteristics and Screen for Predisposing/Precipitating Conditions

Patient data were obtained from a combination of patient interviews, hospital records, and patient-completed questionnaires. The clinical history and baseline characteristics of patients with confirmed NA-SCAD were obtained from patient interviews and extracted from hospital admission records and relevant clinical source documents from physician offices. Baseline cardiovascular risk factors, medication on presentation, hospital presentation, ECG changes, in-hospital events, angiographic, and noninvasive imaging characteristics were
recorded. A detailed patient questionnaire was designed in 2013 and administered to all patients prospectively followed up at our SCAD clinic since.

Potential significant precipitating stressors (Table 1) in the preceding days before the index event were inquired on patient interviews and subsequently also on patient questionnaires. Significant emotional stress and intense physical activities (categorized into aerobic or isometric) were recorded. The active and previous use of hormonal therapy (birth-control pills, estrogen, progesterone, β-human chorionic gonadotropin, and testosterone) was recorded. Other potential precipitating stressors, such as retching and vomiting, straining with bowel movement, the use of recreational drugs (eg, cocaine, amphetamines, and amphetamines), labor, and delivery, were also recorded.

A combination of focused patient interviews and detailed questionnaire was also administered to identify potential relevant predisposing arteriopathies for NA-SCAD (Table 1). Pregnancy history (gravidity and parity), inherited connective tissue disorders, systemic inflammatory conditions predisposing to arteritis, and history of coronary artery spasm were recorded. Postpartum SCAD was defined as occurring early (within 6 weeks of delivery as defined by the World Health Organization) or late (occurring ≤1 year after delivery). Given the dominant association with FMD, patients were routinely screened for noncoronary FMD in ≤3 vascular territories: renal, iliac, and cerebrovascular. Patients identified as possible SCAD prospectively tended to have renal angiography coincident with the index coronary angiogram based on our previous local experience with this condition. In addition, many patients had iliofemoral angiograms performed ipsilateral to their femoral sheath routinely for sheath management. Patients who were not screened for renal or iliac FMD during their index angiography underwent noninvasive computed tomographic angiography or MR angiography. For assessment of cerebrovascular FMD and intracranial aneurysm, noninvasive computed tomographic angiography or MR angiography were performed.

Angiographic SCAD Diagnosis and Classification

All coronary angiogram films were obtained from local and referral hospitals for review at our center. The index admission coronary angiograms were reviewed by 2 experienced interventional cardiologists (J.S., E.A., or D.R.) for the diagnosis and categorization of NA-SCAD. In the absence of previous coronary intervention or trauma, SCAD was confirmed to be present when one of the following 3 criteria were met and categorized:

1. type 1 angiographic SCAD: pathognomonic 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 (Figure 1A);
2. type 2 angiographic SCAD: diffuse (typically >20–30 mm) and usually smooth narrowing that can vary in severity from an inconspicuous mild stenosis to complete occlusion (Figure 1B), plus a. no response to intracoronary nitroglycerin and no atherosclerotic lesions in other coronary arteries or b. repeat coronary angiogram showing angiographic resolution of the dissected segment or previous angiogram showing normal artery, or c. intracoronary imaging with optical coherence tomography or intravascular ultrasound proving the presence of intramural hematoma and double-lumen; or
3. type 3 angiographic SCAD: mimics atherosclerosis with focal or tubular stenosis (Figure 1C and 1D) and requiring optical coherence tomography or intravascular ultrasound to prove the presence of intramural hematoma or double-lumen. The SCAD coronary segment involved was defined by the Bypass Angioplasty Revascularization Investigation classification.

The number of dissected coronary artery segments, location, lesion characteristics (stenosis severity and lesion length), and corresponding wall motion abnormality were recorded. Repeat coronary angiography after the index event was at the discretion of the treating physicians. Results from repeat coronary angiography or intracoronary imaging were recorded.

The diagnosis of SCAD on intracoronary imaging with optical coherence tomography or intravascular ultrasound requires the presence of intramural hematoma and double-lumen. The presence of intimal rupture and thrombi in true or false lumen may also be observed with SCAD but are not necessary for diagnosis.

Diagnosis of FMD

The diagnosis of FMD was made on the basis of angiographic (invasive or noninvasive) imaging because histopathology was not available, and the angiographic appearance depends on the histopathologic subtypes. The most recent American Heart Association scientific statement recommended simplifying the angiographic descriptions to multifocal or focal disease. Multifocal disease is the classic string of beads appearance, which is represented by medial fibroplasia in almost all adults, and the appearance is because of fibromuscular ridges causing arterial stenoses alternating with areas of smooth muscle loss causing arterial dilatation. Focal disease (focal or tubular stenosis irrespective of length) is usually caused by intimal fibroplasia but may also be because of medial hyperplasia or adventitial FMD. Patients may have simultaneous multifocal and focal disease in different...
vascular beds. Other common angiographic findings of FMD include aneurysms, dissections, and tortuosity (with coils, kinks, loops, and bends), but these do not represent angiographic subtypes of disease. We required the presence of multifocal beading/irregular appearance (of varying severity) in ≥1 noncoronary vasculature to make the diagnosis of FMD in our cohort.

Cardiovascular Outcomes

The primary in-hospital outcome is the composite of all-cause mortality, stroke, reinfection,27 cardiogenic shock (requiring medical or mechanical hemodynamic support), 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. The primary long-term outcome is the composite of all-cause mortality, stroke, recurrent MI (including recurrent dissection), congestive heart failure admission, and repeat revascularization, collectively termed major adverse cardiac events (MACE). 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.GRAY

PCI Outcomes Definition

Successful PCI was defined as angioplasty or stenting of the dissected segment with no residual dissection and with final thrombolysis in MI 3 flow. Partially successful PCI was defined as angioplasty or stenting of the dissected segment with residual dissection or stenosis ≤50% of lumen diameter and with final thrombolysis in MI 3 or improved flow. Unsuccessful PCI was defined as angioplasty or stenting of the dissected segment with residual dissection or stenosis >50% of lumen diameter or worsened thrombolysis in MI flow compared with baseline pre-PCI, or extension of dissection requiring bailout CABG. Extension of dissection during PCI was defined as any extension of dissection (increase in dissection length with wiring, balloon angioplasty, or stent placement).

Statistical Analysis

Descriptive statistics were used to assess the baseline characteristics of patients, including demographics, comorbidities, hospital presentation, characteristics of coronary artery angiography, potential predisposing arteriopathies, and involvement with FMD. Continuous variables were summarized as mean±SD or median and interquartile range. Categorical variables were summarized as frequency and percentage. The risk of MACE during follow-up was assessed for prospective and nonprospective groups of patients using Kaplan–Meier method. Statistical analyses were performed with the SPSS software (IBM SPSS version 20; IBM Corp, Armonk, NY) and the R Foundation for Statistical Computing (version 2.36-9, survival package).

Results

We prospectively evaluated 168 patients with NA-SCAD at Vancouver General Hospital; 48 patients were retrospectively identified and 120 patients were prospectively identified. The baseline characteristics of these patients are described in Table 2. The average age was 52.1±9.2 (range, 33–84) years; 57.7% were ≥50 years old and 94.6% were ≥65 years old (Figure 2). The vast majority were women (155/168; 92.3%). These patients had low body mass index (25.0±5.6) and low prevalence of cardiovascular risk factors, except for hypertension and dyslipidemia. NA-SCAD affected all races although the majority was white (81.5%). A sizable proportion of these patients had a history of migraines (37.5%), depression (23.8%), hypothyroidism (11.9%), and was postmenopausal (97/155; 62.3%). Hospital presentations are described in Table 3. All patients presented with MI (troponin-positive), and 8 had ventricular tachycardia or fibrillation in-hospital (1 presented with ventricular fibrillation). The mean peak troponin-I was 17.0±35.2 μg/L (median, 6.0; range, 0.7–200), and mean ejection fraction was 55.8±9.0%. ECG on presentation showed ST-segment elevation in 26.1%, and the remainder had non–ST–segment–elevation MI. With regards to precipitating stressors, intense emotional stress was reported in 40.5% of patients preceding their event; 24.4% reported exercising preceding their pain presentation, with 12.5% reporting lifting heavy weights or doing intense isometric exercises before their event. Less common potential precipitating stressors included 2 patients with severe retching/vomiting, 1 reported straining with bowel movement, 1 reported severe coughing bouts, and 1 was taking metamphetaminne before their SCAD event. Overall, 56.5% reported potential precipitating stressors. Interestingly, among the 13 men with SCAD, 4 participated in intense isometric activities and 1 used metamphetaminne just preceding their SCAD event (38.5%) when compared with only 16/155 (10.3%) women who participated in intense isometric activities. Of the remainder 8 men, 5 of 8 (62.5%) had concomitant FMD as their predisposing arteriopathy (1 also had ulcerative colitis).

The coronary angiographic characteristics are reported in Table 4. The majority (81.0%) of patients had 1 isolated coronary artery dissection, 19.0% had dissection of >1 coronary

Table 2. Baseline Characteristics of Nonatherosclerotic Patients With Spontaneous Coronary Artery Dissection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.1±9.2</td>
</tr>
<tr>
<td>Sex (women)</td>
<td>155 (92.3%)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.3±7.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.5±16.9</td>
</tr>
<tr>
<td>BMI</td>
<td>25.0±5.6</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>137 (81.5%)</td>
</tr>
<tr>
<td>African Canadian</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>East Asian</td>
<td>21 (12.5%)</td>
</tr>
<tr>
<td>South Asian</td>
<td>8 (4.81%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (5.4%)</td>
</tr>
<tr>
<td>Diet controlled</td>
<td>6 (3.6%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>41 (24.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>65 (38.7%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>21 (12.5%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>49 (29.2%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>20 (11.9%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>97/155 (62.3%)</td>
</tr>
<tr>
<td>Migraines</td>
<td>63 (37.5%)</td>
</tr>
<tr>
<td>Depression</td>
<td>40 (23.8%)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CAD, coronary artery disease; and MI, myocardial infarction.
arteries, and 9.5% had dissection involving >1 noncontiguous coronary arteries. SCAD was seen to affect all coronary arterial segments, and the frequency of each arterial segment dissected is shown in Figure 3. The left anterior descending artery was most frequently involved (41.7%), followed by branches of the circumflex artery (ramus and obtuse marginal arteries; 33.7%), branches of the right coronary artery (posterior descending and posterolateral arteries; 21.4%), and branches of the left anterior descending (diagonal and septal arteries; 12.5%). The LM artery was spontaneously dissected in only 1.2%. SCAD typically affected the mid to distal segments of the coronary arteries, with only 8.3% affecting the proximal left anterior descending, circumflex, or right coronary artery. Of note, among 42 patients who had their index coronary angiography via radial access, there were 3 iatrogenic guide-induced dissections (7.1%) unrelated to the presenting NA-SCAD segment: 2 LM dissections requiring emergency CABG and 1 ostial right coronary artery dissection requiring PCI. There was no iatrogenic dissection observed with the femoral approach (n=126). All available dissected segment lesion characteristics (n=203 dissected segments, including recurrent dissections) are described in Table 4. Mean quantitative coronary angiographic stenosis was 78.9±17.6% and mean length was 45.9±22.2 mm. The most commonly observed angiographic appearance was type 2 in 67.0% of dissections. The stereotypical type 1 angiographic SCAD was observed in 29.1%. And 3.9% had type 3 angiographic SCAD mimicking atherosclerosis but proven SCAD with optical coherence tomography or intravascular ultrasound. There was no difference in the baseline characteristics or clinical outcomes according to the angiographic subtypes.

Potential predisposing arteriopathies are described in Table 5. The majority of patients with NA-SCAD (86.3%) had screening of FMD in 3 vascular territories. The most commonly observed predisposing arteriopathy was FMD in 72.0% of patients (although 13.7% were incompletely screened; Table 6); and intracranial aneurysm was observed in 14.0% of patients with NA-SCAD. There were 8.9% multiparous women with ≥ 4 births and 8.3% with ≥ 5 pregnancies. There were 10.7% on active hormonal therapy (estrogen, progesterone, β- human chorionic gonadotropin, testosterone, and birth-control pill),

Table 3. Hospital Presentation of the Patients With Spontaneous Coronary Artery Dissection

<table>
<thead>
<tr>
<th>Hospital Presentation</th>
<th>n=168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td>100%</td>
</tr>
<tr>
<td>Elevated troponin levels</td>
<td>100%</td>
</tr>
<tr>
<td>Peak troponin-I level, μg/L</td>
<td>Median 6.0 (range 0.7–200)</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
</tr>
<tr>
<td>ST elevation</td>
<td>44 (26.1%)</td>
</tr>
<tr>
<td>ST depression or T inversion</td>
<td>50 (29.7%)</td>
</tr>
<tr>
<td>Nonspecific ST-T changes</td>
<td>23 (13.7%)</td>
</tr>
<tr>
<td>Normal ST-T segments</td>
<td>37 (22.0%)</td>
</tr>
<tr>
<td>VT/VF (ICD or cardioversion)</td>
<td>6 (3.6%)</td>
</tr>
<tr>
<td>Precipitating factors</td>
<td></td>
</tr>
<tr>
<td>Emotional stress</td>
<td>68 (40.5%)</td>
</tr>
<tr>
<td>Exercise related</td>
<td>41 (24.4%)</td>
</tr>
<tr>
<td>Heavy isometric activities</td>
<td>21 (12.5%)</td>
</tr>
<tr>
<td>Retching/vomiting/bowel movement/cough</td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td>Metamphetamine</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>None identified</td>
<td>72 (42.9%)</td>
</tr>
<tr>
<td>EF (mean±SD)</td>
<td>55.8±9.0%</td>
</tr>
<tr>
<td>EF&lt;50%</td>
<td>29 (17.3%)</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; ICD, implantable cardioverter-defibrillator; and VT/VF, ventricular tachycardia/ventricular fibrillation.

Figure 2. Histogram showing the age distribution.
and 8.9% had associated systemic inflammatory conditions (ulcerative colitis, Crohn disease, rheumatoid arthritis, celiac disease, and Graves disease). Postpartum SCAD (2.4%) and connective tissue disorder (1.2%) were uncommon. More than 1 potential predisposing arteriopathy was present in 13.1% of patients. Only 20.8% were deemed idiopathic although 23 of 35 of these cases were incompletely screened for FMD.

The majority of patients (134/168; 79.8%) were treated conservatively on initial presentation with SCAD (Figure 4). Of these, the recurrent in-hospital MI event rate was 4.5% (6/134), with 1 requiring CABG for spontaneous retrograde LM dissection, 2 underwent emergent PCI (both unsuccessful), and 3 were treated conservatively. Among conservatively managed patients who underwent early repeat coronary angiography <20 days after SCAD (n=9; median, 5 days; range, 2–19 days), angiographic healing did not occur yet. However, among conservatively managed patients who underwent elective repeat angiography ≥26 days later (74 coronary angiograms and 5 CT angiograms), all 79 showed spontaneous angiographic healing (median, 161 days; range, 26–4195 days; Figure 5).

Five patients were initially treated with fibrinolysis, of which 3 subsequently underwent PCI. Six underwent CABG: 1 had CABG as initial therapy (needed concomitant valve surgery for aortic stenosis), 1 had emergency CABG for retrograde spontaneous LM dissection, 3 had bailout CABG after failed PCI (including 2 with radial guide-induced LM dissection), and 1 underwent late CABG for diffuse in-stent restenosis with PCI. Twenty-eight underwent PCI as initial therapy; additional 5 underwent PCI after fibrinolysis or failed conservative therapy. Of the 33 patients who underwent PCI during their index hospitalization (Figure 6), 36.4% (12/33) were unsuccessful, 27.3% (9/33) were partially successful, and 36.4% (12/33) were successful. Among the successful and partially successful PCI, 57.1% had procedural extension of dissection, including 14.3% (3/21) with dissection into LM requiring stenting; 2 had extension of dissections after PCI requiring repeat PCI in-hospital. Overall, 4 of 33 patients with PCI required CABG, 2 of 33 had stent thrombosis, and 5 of 21 had severe in-stent restenosis at follow-up. Only 30.3% of the

### Table 4. Coronary Artery Angiographic Characteristics in Patients With SCAD

<table>
<thead>
<tr>
<th>SCAD angiographic characteristics</th>
<th>n=168</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCAD involving &gt;1 coronary arteries</td>
<td>32 (19.0%)</td>
</tr>
<tr>
<td>Noncontiguous arteries involved</td>
<td>16 (9.5%)</td>
</tr>
<tr>
<td>SCAD lesion characteristics</td>
<td>203 dissections</td>
</tr>
<tr>
<td>Type 1 angiographic SCAD</td>
<td>59 (29.1%)</td>
</tr>
<tr>
<td>Type 2 angiographic SCAD</td>
<td>136 (67.0%)</td>
</tr>
<tr>
<td>Type 3 angiographic SCAD</td>
<td>8 (3.9%)</td>
</tr>
<tr>
<td>Angiographic stenosis severity (mean±SD)</td>
<td>78.7±17.9%</td>
</tr>
</tbody>
</table>

### Table 5. Potential Predisposing Arteriopathies

<table>
<thead>
<tr>
<th>Predisposing Arteriopathies</th>
<th>n=168</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMD</td>
<td>121 (72.0%)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>4 (2.4%)</td>
</tr>
<tr>
<td>Systemic inflammatory condition</td>
<td>15 (8.9%)</td>
</tr>
<tr>
<td>Connective tissue disorder</td>
<td>2 (1.2%)</td>
</tr>
<tr>
<td>Multiparous (≥4 births)</td>
<td>15 (8.9%)</td>
</tr>
<tr>
<td>Grand multiparity (≥5 births)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Grand multigravida (≥5 pregnancies)</td>
<td>14 (8.3%)</td>
</tr>
<tr>
<td>On hormonal therapy</td>
<td>18 (10.7%)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>35 (20.8%)</td>
</tr>
</tbody>
</table>

FMD indicates fibromuscular dysplasia.

---

Figure 3. Frequency of spontaneous coronary artery dissection (SCAD) affecting different coronary arterial segments. d indicates distal; LAD, left anterior descending; LCX, left circumflex; LM, left main; m, mid; OM, obtuse marginal; p, proximal; PDA, posterior descending artery; PL, posterolateral; and RCA, right coronary artery.

Figure 4. Frequency of spontaneous coronary artery dissection (SCAD) affecting different coronary arterial segments. d indicates distal; LAD, left anterior descending; LCX, left circumflex; LM, left main; m, mid; OM, obtuse marginal; p, proximal; PDA, posterior descending artery; PL, posterolateral; and RCA, right coronary artery.
PCI procedures had successful and durable results, without need for LM stenting, repeat target-lesion revascularization, stent thrombosis, or in-stent restenosis.

In-hospital major adverse events were as follows. There was no in-hospital mortality. There were 4 (2.4%) transient ischemic attack or stroke events (1 was a simultaneous vertebral dissection) in-hospital. There were 8 (4.8%) in-hospital recurrent MI. Eight (4.8%) had ventricular tachycardia/ventricular fibrillation, with 6 requiring defibrillation or permanent defibrillator implantation. Repeat or unplanned in-hospital revascularization occurred in 8 patients (4.8%). Two patients (1.2%) required intra-aortic balloon pump in-hospital.

The median follow-up was 6.9 years in the retrospective cohort and 0.8 years in the prospective cohort. The Kaplan–Meier cumulative MACE event curves are shown in Figure 7. Only 1 patient was lost to follow-up. The 2-year MACE rates were 16.9% (95% confidence interval, 5.5–26.9%) in the retrospective group and 10.4% (95% confidence interval, 2.0–18.2%) in the prospective group. Overall, long-term MACE after the initial hospitalization occurred in 8 patients (4.8%). Two patients (1.2%) required intra-aortic balloon pump in-hospital.

The median follow-up was 6.9 years in the retrospective cohort and 0.8 years in the prospective cohort. The Kaplan–Meier cumulative MACE event curves are shown in Figure 7. Only 1 patient was lost to follow-up. The 2-year MACE rates were 16.9% (95% confidence interval, 5.5–26.9%) in the retrospective group and 10.4% (95% confidence interval, 2.0–18.2%) in the prospective group. Overall, long-term MACE after the initial hospitalization occurred in 34 (20.2%) patients. There were 4 (2.4%) deaths (1 cardiovascular and 3 noncardiovascular). Recurrent MI occurred in 26 (15.6%) patients, of which 22 (13.1%) were because of recurrent SCAD events. There was 1 (0.6%) stroke event and no admission for heart failure. Subsequent revascularization was required in 11 (6.5%) patients. Of note, 13 (7.7%) required repeat hospitalization for troponin-negative chest pains.

**Discussion**

NA-SCAD is a poorly understood condition, and we sought to evaluate the prevalence of potential predisposing arteriopathies and precipitating stressors, as well as the outcome after conservative or revascularization therapy. We prospectively evaluated 168 patients with NA-SCAD at Vancouver General Hospital, which elucidated several new and important insights about this illness. To our knowledge, this is the largest cohort of patients with NA-SCAD reported. Contrary to previous belief, NA-SCAD did not predominantly affect young women in our contemporary series; in fact, 58% were aged ≥50 years and 62% were postmenopausal. We also found that NA-SCAD was commonly associated with potential predisposing arteriopathies and precipitating stressors, as opposed to being mostly idiopathic as previously thought. Through detailed angiographic review, we found that the majority of NA-SCAD did not have the stereotypical angiographic appearance of arterial wall stains, but rather, the most common appearance was a diffuse long and smooth stenosis (type 2 SCAD). Our findings on cardiovascular outcomes also confirmed that a conservative management strategy for stable patients is viable and strongly associated with spontaneous angiographic healing in a large number of patients. This treatment strategy is also preferred given the suboptimal outcomes and procedural complications with PCI for NA-SCAD. And finally, long-term follow-up revealed high cardiovascular event rates, especially with regards to recurrent dissection and MI.

The demographics of our contemporary NA-SCAD cohort are noteworthy. The majority affected were women (92.3%), with broad age range from 33 to 84 (average age, 52.1) years. Although 95% were aged <65 years, 38% were ≥60 years and 62% were postmenopausal. Previous studies have shown that NA-SCAD had a predilection for young women (often defined as age, <50 years), but it is increasingly being recognized that older women may also be affected. In the Mayo Clinic series, the average age of their 87 patient-cohort was 42.6 (range, 18–78) years. In the series by Vanzetto, the average age of their 23 patient-cohort was 46 (range, 30–69) years, and the
incidence of SCAD was particularly high in women aged <50 years, presenting with acute coronary syndrome (10.8%). In the series by Alfonso et al, among their 27 NA-SCAD cohort, their average age was older at 52 years, similar to our study. Our group also reported that NA-SCAD was the cause of MI in 24% of women aged ≤50 years undergoing angiography for MI. The proportion of MI because of NA-SCAD in women aged >50 years remains unknown but is suspected to be much lower than younger women, especially because there is an age-dependent increase in MI frequency related to atherosclerosis. Thus, although proportionally it is more likely that NA-SCAD is the underlying cause of MI in younger women, the demographics from our study imply that NA-SCAD in older women is also not rare and should be considered in the differential for MI cause.

Although previous studies indicated that most NA-SCAD cases were idiopathic in origin, we recently discovered a strong and frequent association with FMD on routine screening. In our current NA-SCAD cohort, we found concomitant FMD in 72%, even though 14% had not been fully screened for FMD in 3 vascular territories. We suspect that the actual proportion with concomitant FMD will be higher once complete screening is attained, with projected estimate of 70% to 80% for patients with NA-SCAD. Our diagnosis of FMD seems higher than other centers because of the use of conventional catheter angiography in a large proportion of our patients, typically performed during their index coronary angiography. Noninvasive computed tomographic angiography and MR angiography have lower spatial resolution and may miss mild FMD changes. The prevalence of other potential predisposing arteriopathies (Table 5) was much less frequent, including hormonal therapy (11%), systemic inflammatory condition (9%), multiparity with ≥4 births (9%), and postpartum (2%). Other series from Alfonso et al (4%) and Tweet et al (8%) have also reported low incidence of postpartum cases. These pathologies had been previously linked with NA-SCAD, and several had autopsy reports showing histological coronary arterial wall abnormalities at the site of dissection implicating cause. In our cohort, these predisposing arteriopathies are presumed to be causative for the NA-SCAD events; however, the evidence remains circumstantial because histological proof is not available.

With routine questioning on history and questionnaire, we found that 57% of our patients had precipitating stressors preceding their SCAD. Approximately 40% reported being emotionally stressed (eg, death in the family, breakdown of marriage, arguments, and job stress) and 24% reported physical activities preceding their event. Of note, 13% participated in...
isometric exercises or lifted heavy items the day of, or within
days before their SCAD. Less frequently reported stressors
included retching/vomiting, severe coughing, and intense
straining with bowel movement. These activities have the commonal-
ity of intense bearing down Valsalva-like transient increases in
intrathoracoabdominal pressures, which have been reported to
precipitate SCAD events, especially those with underlying
artiopathies. Interestingly, men seemed to more commonly
have physical stressors of intense isometric activities or metam-
phatamine use preceding their event (39%) when compared with
women (10%), which was also previously suggested by Tweet
et al. Emotional stress is speculated to have different trigger
pathophysiology, presumably related to stress catecholamines.
One hypothesis is that catecholamine surge can increase arte-
rial shear stress leading to intimal rupture or disruption of vasa
vasorum, probably through increases in myocardial contractil-
ity or vasospasm. Whether chronic catecholamine elevation can
induce structural changes in the arterial wall is unknown. The
underlying arteriopathies. Thus, the interplay of precipitating
story, and their SCAD events occurred irrespective of
underlying arteriopathies. Thus, the interplay of precipitating
and predisposing conditions for SCAD is complex and not fully
understood and warrants further prospective evaluation.

Our angiographic finding that the most common SCAD
appearance is diffuse long and smooth stenosis (type 2 angi-
ographic SCAD) without obvious intimal disruption is compat-
ible with previous reports with intracoronary imaging. In our
large angiographic series of 203 coronary dissected segments,
we found that type 2 constituted 67% of SCAD appearance. The
stereotypical contrast arterial wall stain of SCAD was present in
only 29% of dissected arteries. Much less frequent was focal/
tubular stenosis that mimicked atherosclerosis although this type
3 SCAD appearance may have been underdiagnosed because of
misinterpretation as atherosclerosis, especially if intracoronary
imaging was not done. Therefore, if angiographers rely solely
on the presence of contrast wall stain to make the diagnosis of
SCAD, they would miss >70% of angiographic SCAD. Another
important angiographic characteristic is the long average length
of 46 mm as measured on quantitative coronary angiography.
This is in keeping with previous observation that NA-SCAD
lesions have longer dissected lengths when compared with
atherosclerosis, with the presumption that medial atrophy and
scarring of atherosclerosis limits extension of dissection. The
observation that guide-induced iatrogenic dissections occurred in
3 of 42 (7.1%) radial-approach angiograms performed, includ-
ing 2 extensive LM dissections requiring emergent CABG, were
alarming. These dissections occurred at sites unrelated to the
presented SCAD and highlighted the coronary arterial fragility
in these patients prone to dissections. Thus, meticulous angiog-
ographic techniques should be practiced in patients with SCAD,
avoiding deep catheter intubation, with careful attention to press-
sure dampening, and performing gentle coronary injections.

Many of our patients had repeated coronary angiograms after
their index event, either for recurrent chest pains or physi-
cian preference to assess the dissected segments. Angiograms or
computed tomographic angiography performed ≥4 weeks after
their SCAD event showed angiographic healing in all cases (79/79) that were managed conservatively. This eluci-
dates the natural history of SCAD confirming that dissected
arteries tend to heal spontaneously, corroborating previous
smaller reported series that also showed frequent occurrence of
spontaneous healing. Furthermore, in our cohort of conserva-
tively managed patients, in-hospital recurrent MI occurred in
only 4.5% (6/134), and only 3/6 underwent subsequent in-
hospital revascularization. This justifies an initial conservative
management for stable patients with SCAD without evidence of
ongoing ischemia or hemodynamic compromise, which has
been endorsed by our group and others (Alfonso et al and
Tweet et al). This approach is especially practical in light of
the dismal outcomes with PCI for SCAD lesions, as shown by
our cohort and others. The technical success (complete and
partial success) rate with PCI was only 64%, of which 57%
had extensive of dissection during PCI, and in total only 30%
had successful and durable PCI results. In the Mayo Clinic
series, technical failure with PCI was similar at 35%. The
long-term results with CABG had also been reportedly disap-
pointing, where >70% of grafts were found to be occluded at
follow-up. This poor result probably reflects the natural his-
tory of spontaneous healing of dissected arteries, culminating
in eventual graft failure from competitive flow, as opposed to
technical challenges of approximating dissected arterial lay-
ers. In life-threatening cases, CABG may be the only means
of establishing coronary flow and salvaging ischemic myocar-
dium, aside from more aggressive measures, such as cardiac
transplantation. Consolidating these outcome data, we propose
a management algorithm favoring conservative therapy, unless
there are features of ongoing/recurrent ischemia, hemody-
amic and electric instability, and LM dissection (Figure 8).
A conservative algorithm was also proposed by Alfonso
et al, but we have expanded the revascularization indications to
include hemodynamic/electric instability and anatomic con-
siderations and provided practical guidelines on selecting PCI
versus CABG. In addition, because of the potential (albeit low)
recurrent risk of in-hospital MI because of extension of dissec-
tion, we also recommend that conservatively managed patients
should be observed in hospital for 2 to 4 days, until symptom
resolution and verification of clinical stability.

The optimal medical management of patients with SCAD
has unfortunately not been explored given the rarity of this
condition. No prospective randomized data are available to
guide medical management and it is uncertain if the standard
care of pharmacotherapy is appropriate for many patients
with SCAD. We previously summarized the limited evidence available and concluded that patients
with SCAD should remain on aspirin and β-blocker long
term, which we have adopted as our standard treatment rec-
ommendation. Additional antiplatelet therapy with clopido-
grel is also typically administered for 1 to 12 months after the
initial SCAD event, and often discontinued if angiographic
healing was demonstrated. Angiotensin-converting enzyme
inhibitor (or angiotensin-receptor blocker) is routinely admin-
istered only in patients with significant left ventricular dys-
function. Statin therapy is only administered in patients
with pre-existing dyslipidemia, given some concern of higher
SCAD recurrence with statins, albeit from small retrospec-
tive data. We have launched a small randomized controlled
study comparing angiotensin-converting enzyme inhibitor
and statin versus placebo for patients with SCAD (Statin and
Angiotensin-Converting Enzyme Inhibitor on Symptoms in Patients With SCAD [SAFER-SCAD] study; NCT02008786), which will hopefully help guide medical management for this relatively data-void condition. The use of nitroglycerin or calcium channel blockers for SCAD has not been studied.

We segregated the long-term cardiovascular outcomes according to our retrospective or prospective cohorts because the follow-up duration was disparate (median follow-up, 6.9 years in the retrospective group and 0.8 years in the prospective group). Overall, long-term MACE were not infrequent; in particular, recurrent MI occurred in 16% of patients. The majority was because of recurrent dissection in another coronary segment (13% recurrent SCAD events). Longer term follow-up, especially of our prospectively identified cohort, would be important to clarify the long-term cardiovascular outcomes of our patients with NA-SCAD. We also recently launched the Canadian SCAD Study (NCT02188069) sponsored by the Canadian Institutes of Health Research, which will enroll 750 to 1000 patients with NA-SCAD prospectively throughout Canada to evaluate the natural history of this condition.

Limitations
Although our study is the largest SCAD cohort reported to date, the overall sample size is relatively small, and our results may be subject to sampling and referral bias. Although we currently advocate a conservative approach for managing acute SCAD patients, we could not control or elucidate the indications for revascularization in our cohort, which is based on physician preference and presumed clinical instability. Such bias limits our ability to compare outcomes according to revascularization strategies. Nevertheless, our patient-cohort is prospectively evaluated, and the outcomes observed represent the natural history of this complex disease with numerous management challenges. A smaller proportion (29%) of our cohort was retrospectively identified and may introduce bias when evaluating outcome event rates. Thus, we have segregated the long-term cardiovascular outcomes according to retrospectively and prospectively identified patients. At this juncture, our prospectively identified cohort only has 0.8-year median long-term follow-up, and longer prospective follow-up is required to clarify the outcomes in this prospective group. We have attempted to screen predisposing arteriopathies and precipitating conditions in all patients, but there remains ≈14% of patients not having complete FMD screen. As well, although history and physical examinations were performed in all patients, we did not routinely perform laboratory markers of inflammation or genetic analysis for connective tissue disorders. Thus, the actual prevalence of predisposing arteriopathies may be underestimated in our cohort. In the subgroup of patients with type 2 angiographic SCAD, ≈2 of 3 had intracoronary imaging that proved SCAD or repeat angiography that showed subsequent healing. Although there is a possibility of overdiagnosis in a small proportion of the remainder 1 of 3 in the type 2 category, these stenosis were diffuse and smooth that were atypical for atherosclerosis, and we were vigilant in excluding typical atherosclerotic changes (eg, calcification, involvement of bifurcation/ostia, and aneurysm) in other coronary arterial segments. Our current 168 patient-cohort included the original 50 patients previously reported; there was no difference in the baseline characteristics or clinical outcomes between the first 50 patient-cohort and the subsequent 118 patient-cohort.

Conclusions
NA-SCAD predominantly affects women, and a large proportion is postmenopausal. The majority of patients have underlying FMD and precipitating emotional or physical stressors. Conservative therapy for stable patients is associated with low in-hospital events and spontaneous angiographic healing at ≥4 weeks. Long-term cardiovascular events are common, necessitating ongoing cardiovascular assessments. Larger prospective long-term follow-up studies to evaluate cardiovascular outcomes further, and correlation of such events to predisposing arteriopathies and revascularization strategies, would be important.
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Spontaneous Coronary Artery Dissection: Association With Predisposing Arteriopathies and Precipitating Stressors and Cardiovascular Outcomes

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