JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 8, 2020

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Spontaneous Coronary Artery Dissection

JACC State-of-the-Art Review

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ABSTRACT

Over the past decade, spontaneous coronary artery dissection (SCAD) has emerged as an important cause of myocardial infarction, particularly among younger women. The pace of knowledge acquisition has been rapid, but ongoing challenges include accurately diagnosing SCAD and improving outcomes. Many SCAD patients experience substantial post-SCAD symptoms, recurrent SCAD, and psychosocial distress. Considerable uncertainty remains about optimal management of associated conditions, risk stratification and prevention of complications, recommendations for physical activity, reproductive planning, and the role of genetic evaluations. This review provides a clinical update on the diagnosis and management of patients with SCAD, including pregnancy-associated SCAD and pregnancy after SCAD, and highlight high-priority knowledge gaps that must be addressed. (J Am Coll Cardiol 2020;76:961–84) © 2020 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

Over the past decade, there has been a paradigm shift in clinical appreciation of spontaneous coronary artery dissection (SCAD), a nonatherosclerotic, nontraumatic cause of acute coronary syndrome and sudden cardiac death. Recent practice-changing data have informed how this condition is diagnosed and managed. Consensus statements from the United States and Europe (1,2) affirm that SCAD is no longer so "rare" such that it cannot be studied; however, despite improved recognition of SCAD, high-level evidence-based guidance for optimal acute and long-term care are lacking. Available data to guide diagnostic and patient management decisions are still mostly retrospective, observational, and often confounded by selection, survival, and reporting biases. However, recent collaborative multicenter and multinational investigations promise to provide more evidence to inform clinical care.

This review aims to build upon prior consensus statements, incorporate recent evidence to advance understanding of the pathophysiology of SCAD, highlight the importance of and optimal means to accurately diagnose acute SCAD, and discuss controversies and current practice in early post-SCAD management. Developments in our understanding of genetic predilections for SCAD highlight the need for development of molecular, cellular, and whole

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received March 18, 2020; revised manuscript received May 11, 2020, accepted May 26, 2020.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.05.084

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

CTA = computed tomography angiography

EVA = extracoronary vascular abnormality

FMD = fibromuscular dysplasia

IMH = intramural hematoma

PCI = percutaneous intervention

P-SCAD = pregnancy-associated spontaneous coronary artery dissection

OCT = optical coherence tomography

SCAD = spontaneous coronary artery dissection

animal model systems to gain further mechanistic insight into the pathobiology of SCAD. Finally, top priority topics are highlighted to address the pressing clinical and research questions in the care of patients with SCAD.

EPIDEMIOLOGY, PATHOPHYSIOLOGY, AND GENETICS

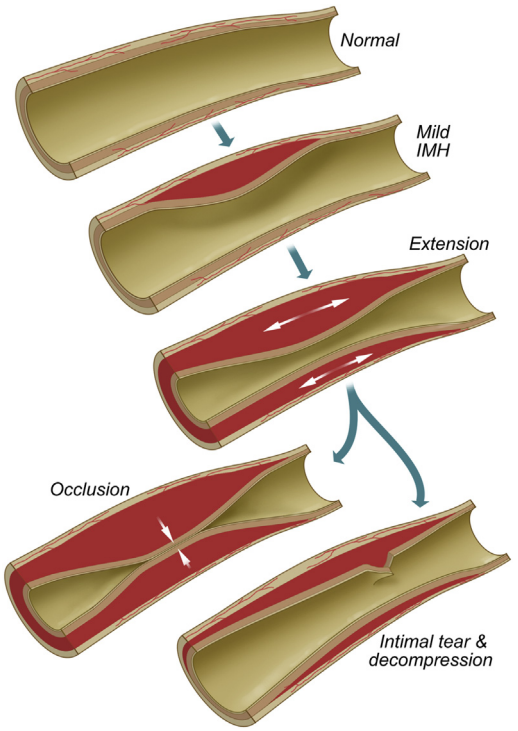
EPIDEMIOLOGY. The "typical" SCAD patient is a middle-aged woman with few traditional cardiovascular risk factors, but acute myocardial infarction (AMI) due to SCAD has been observed from the late teens to the ninth decade of life. SCAD is likely influenced by a combination of factors that include sex; hormonal fluctuations; underlying arteriopathies; genetics; and environmental, physical, and emotional precipitants. Women comprise 87% to 95% of SCAD with a mean age of presentation between 44 and 53 years (3-5). Although the overwhelming majority of patients reported in these large series have been white, the most racially and ethnically diverse, population-based cohort (45% Hispanic Americans, 16% Blacks) found that the presentation and outcomes are similar in these other populations (6). This suggests that rather than certain populations being at lower risk for SCAD, they instead are under-represented in most current registries, possibly due to recruitment methodologies, referral bias, and the racial and ethnic composition of populations near recruiting centers. Although patients with SCAD have lower rates of traditional cardiovascular risk factors such as hypertension, hyperlipidemia, and tobacco use compared with patients with atherosclerotic AMI (3,5-8), prevalence of hypertension (32% to 37%) and hyperlipidemia (20% to 35%) in SCAD patients (3,5,8) is similar to age and sex-matched populations (9).

Single-center studies have estimated a prevalence of SCAD as high as 4% of patients presenting with acute coronary syndrome (ACS) (10) and the underlying cause of up to 35% of all ACS cases in women ≤50 years of age (11,12). Efforts to estimate population-based SCAD prevalence and incidence have been limited by dependence on administrative databases, lack of clinical details, incomplete exclusion of atherosclerotic dissections, and obsolete angiographic diagnostic criteria. Also missing are patients who died prior to diagnosis and patients without coronary imaging. With these caveats in mind, 2 studies spanning a timeframe when intramural hematoma was not typically identified as SCAD found that prevalence of SCAD was 0.78% among 26,598 patients discharged with a principal diagnosis of AMI in California (2006 to 2016) (6,13) and among 0.98% of 752,352 women presenting with AMI (2009 to 2014) (13).

HIGHLIGHTS

- SCAD is an important cause of MI, with unique associations and outcomes.
- Chest pain after SCAD is common; an initial noninvasive approach for stable patients is preferred.
- Evidence remains sparse for counseling about recurrence risk, physical activity, mental health, and reproductive issues.
- Prospective and collaborative research across centers and geography are needed to advance the science.

FIGURE 1 Pathogenesis and Natural History of Spontaneous Coronary Artery Dissection



An intramural hematoma (IMH) forms, which most commonly resorbs and "heals." Early IMH extension can result in vessel occlusion or develop an intimal tear resulting in decompression and resumption of flow. D.F. © MAYO 2020. Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

TABLE 1 Susceptibility Genes for Spontaneous Coronary Artery Dissection

First Author, Year (Ref. #)	Gene	Protein Function	Identified Variants	Subjects	Study Design
Fahey et al., 2018 (21)	*F11R* (F11 receptor)	Regulator of tight junction assembly	Rare missense	Familial SCAD (affected mother and daughter)	Whole exome sequencing, bioinformatics, cosegregation
Turley et al., 2019 (22)	*TLN1* (talin 1)	Links actin cytoskeleton to extracellular matrix	Rare missense	Familial SCAD (affected brother, sister, and aunt); sporadic SCAD cohort (n = 675); predominantly white females	Whole exome sequencing, bioinformatics, cosegregation, gene-targeted case-control burden testing, mutation scanning
Sun et al., 2019 (23)	*TSR1* (TSR1 ribosome maturation factor)	Orchestrates RNA processing	Rare missense, nonsense, frameshift	Sporadic SCAD discovery cohort (n = 85); sporadic SCAD replication cohort (n = 53); predominantly Han Chinese men with CAD risk factors	Whole exome sequencing, genome-wide gene-based case-control association testing × 2, replication
Adlam et al., 2019 (24)	*PHACTR1* (phosphatase and actin regulator 1) *EDN1* (endothelin 1)	Regulator of actin cytoskeleton Circulating vasoactive peptide	Common regulatory single nucleotide variant	Sporadic SCAD cohorts (n = 1,055); predominantly white women from Europe, Australia and the United States	Multicenter, targeted genotyping of FMD risk allele, case-control association testing

CAD = coronary artery disease; FMD = fibromuscular dysplasia; RNA = ribonucleic acid; SCAD = spontaneous coronary artery dissection.

PATHOPHYSIOLOGY. SCAD is an acute coronary event relating to development of hematoma within the tunica media leading to separation of the intima or intima-medial complex from the underlying vessel and compressing the true lumen causing ischemia and AMI. Two hypotheses have been proposed to explain the pathophysiological process: the "inside-out" hypothesis suggests that blood enters the subintimal space from the true lumen after development of an endothelial-intimal disruption or "flap"; and in the "outside-in" hypothesis, the hematoma arises de novo in the media, possibly from disruption of traversing microvessels (**Figure 1**) (14,15). Three lines of evidence favor the "outside-in" hypothesis: 1) most SCAD cases show no communication between true and false lumens (14,16,17); 2) serial angiograms performed early after SCAD indicate that intramural hematoma precedes development of intimal dissection (14); and 3) optical coherence tomography (OCT) imaging suggests the false lumen is pressurized and that observed fenestrations may arise from rupture of the false lumen into the true lumen rather than vice versa (17). Earlier observations of increased adventitial vasa vasorum density after SCAD, whether a causal factor or a response to injury, have not been confirmed in a more recent series (17). Although the majority of SCADs are likely due to an "outside-in" mechanism, the SCAD phenotype may result from more than 1 pathophysiological sequence.

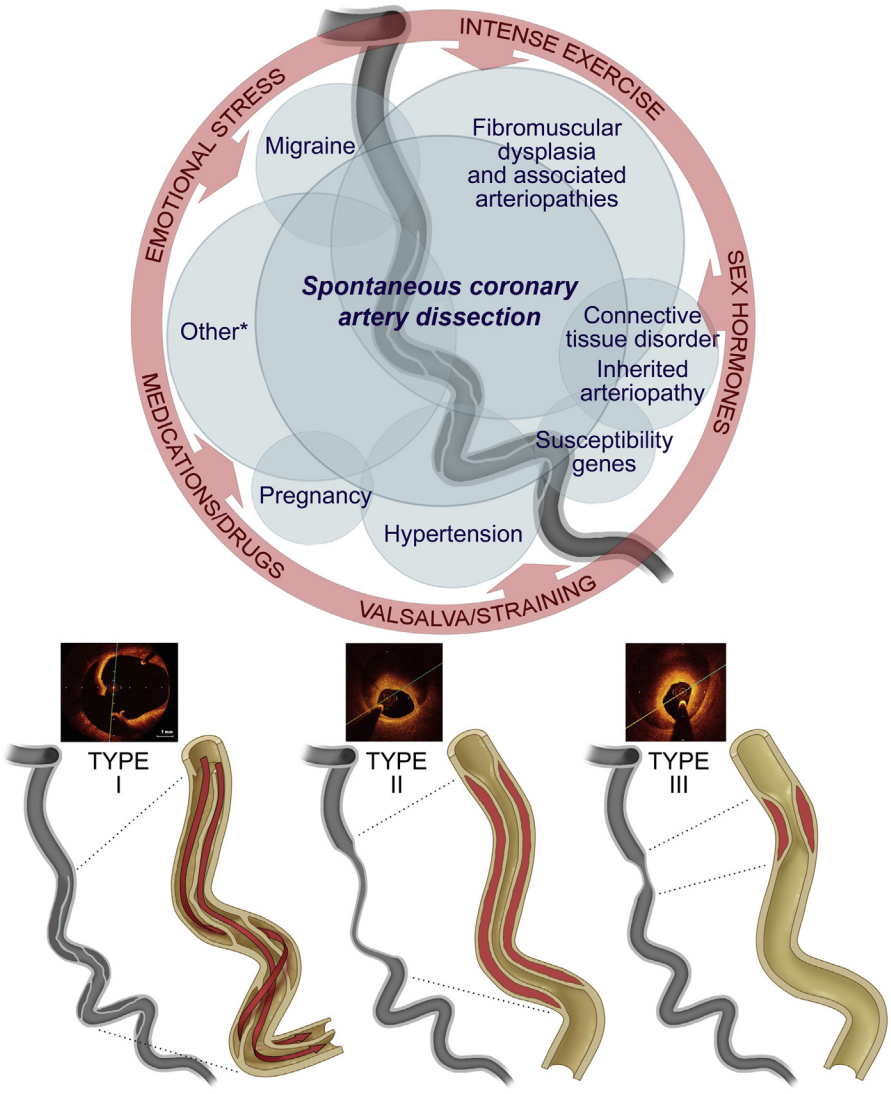
GENETICS. Research to identify genetic determinants of SCAD, enabled by phenotypically characterized patient cohorts and rare familial cases coupled with advanced genomic technologies and bioinformatics, is at an early stage (**Table 1**). A monogenic basis for SCAD is less evident than for heritable vascular disorders like Marfan syndrome, which displays multigenerational autosomal dominant inheritance pattern (18,19). Discovery of pathogenic variants in known genes for connective tissue disorders and aortopathy syndromes such as Marfan, Loeys-Dietz, and Ehlers-Danlos, may have significant clinical and counseling implications for the individual and his/her family and

TABLE 2 Pregnancy-Associated Spontaneous Coronary Artery Dissection

First Author, Year (Ref. #)	N	Design	Mean ± Age at SCAD (yrs)	Mean Gravidity	Left Main SCAD (%)	Multivessel SCAD (%)	Cardiac Function
Higgins et al., 2013 (96)	47	Case series	33.5 ± 5.3	2.7	36	34	Hemodynamically unstable*: 21%
Havakuk et al., 2017 (32)	120	Case series	34 ± 4	–	36	40	LVEF <40%: 44%
Koller et al., 1998 (97)	43	Case series	33.5 ± 5.3	3.1	18	18	–
Koul et al., 2001 (31)	58	Case series	33	2.1	24	40	–
Tweet et al., 2017 (30)	54	Registry cohort	35 ± 4	3.2	24	33	LVEF <35%: 26%
Faden et al., 2016 (38)	79	Population-based cohort†	33 ± 5.2	–	–	–	Cardiogenic shock: 20%

*3 patients underwent cardiac transplantation in this series. †National Inpatient Sample administrative database
LVEF = left ventricular ejection fraction; SCAD = spontaneous coronary artery dissection.

CENTRAL ILLUSTRATION Associated Conditions, Inciting Factors, and Angiographic Diagnosis of Spontaneous Coronary Artery Dissection



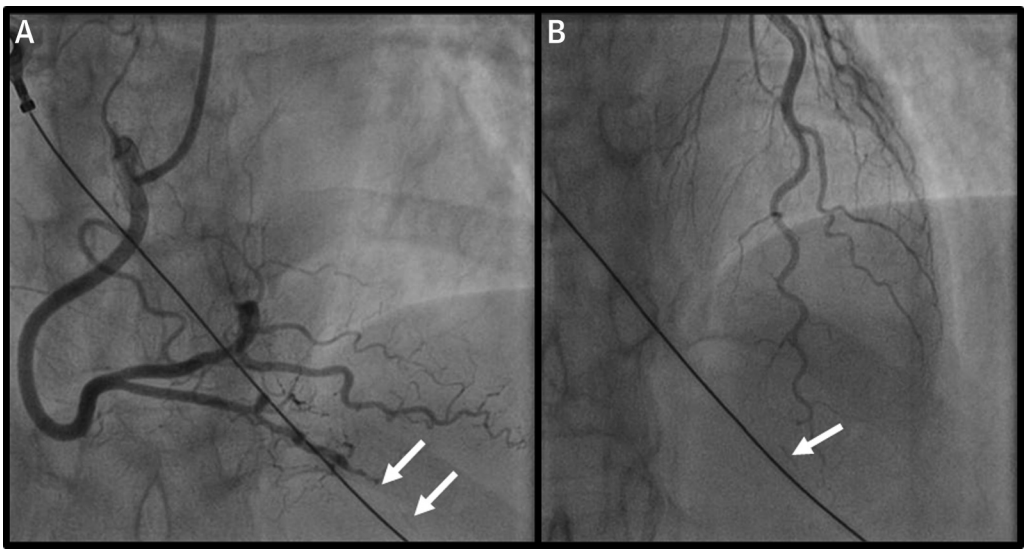
Hayes, S.N. et al. J Am Coll Cardiol. 2020;76(8):961–84.

Spontaneous coronary artery dissection often occurs in the setting of 1 or more overlapping conditions **(blue circles)**, often with a precipitant or trigger **(red outer ring)**. Angiographic, anatomic, and optical coherence tomographic representation of spontaneous coronary artery dissection types 1 to 3 (bottom). *Includes idiopathic, systemic inflammatory conditions, coronary vasospasm, and other less common associated conditions.

is often assessed in patients after SCAD; however, these account for only a small proportion (5% to 9%) of events. Notwithstanding, genetic underpinnings of SCAD are inferred by a low burden of traditional coronary artery disease risk factors and directly implicated by reports of SCAD in 2 or more first-, second-, or third-degree relatives (20). Whole exome sequencing in familial SCAD, while accounting for <1% of cases, provides a unique opportunity to identify segregating culprit gene variants with major effect size on the disease phenotype.

On the other hand, case-control cohort studies can reveal common functional single nucleotide variants that are associated with disease susceptibility (21–24).

FIGURE 2 **Distal Coronary Artery Occlusion of Uncertain Etiology**



Occlusion of the very distal posterior descending artery with upstream narrowing **(A, arrows)** suggests dissection rather than embolism with both antegrade and retrograde filling of the occluded vessel **(B, arrow)**. Intracoronary imaging to confirm the diagnosis is neither possible nor safe.

The genetic investigations published to date do not provide an explanation for sex differences in SCAD susceptibility. The striking over-representation of SCAD in women may be attributable to autosomal susceptibility genes that exhibit sex-specific regulation, for example, genes with estrogen response elements, or intrinsic, gene-independent differences in coronary biology in women.

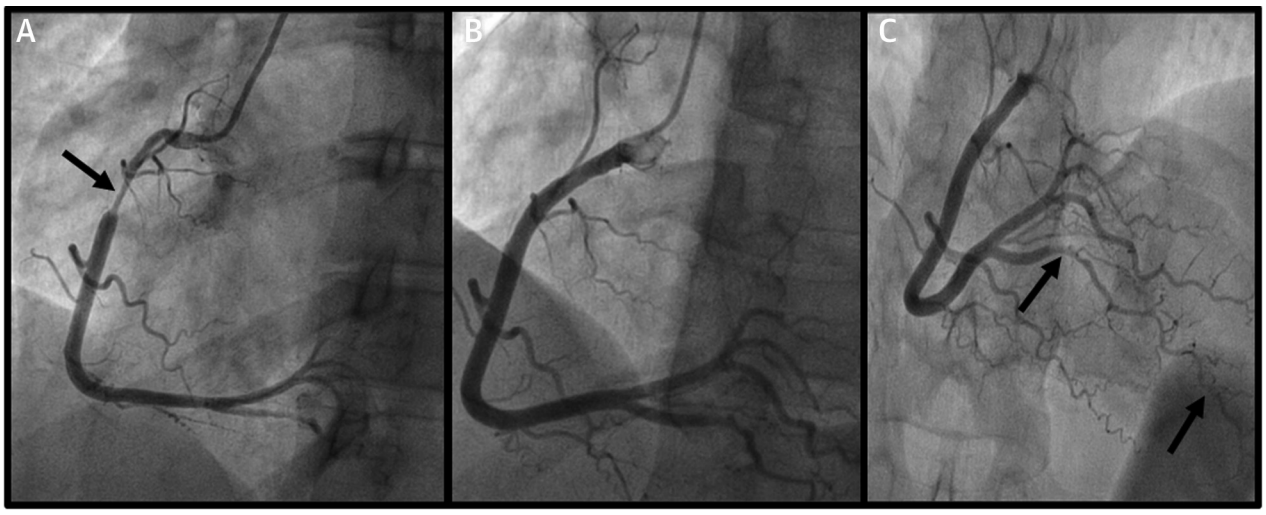
Future genetic investigations in SCAD should focus on the subgroups most likely to be enriched for major-effect genetic variants, including familial SCAD, recurrent SCAD, and SCAD in the young. It will be of interest to determine if less-common forms of SCAD, for example, SCAD in men or in older, postmenopausal women, have distinct susceptibility genes. The finding of a common SCAD risk allele at the *PHACTR1/EDN1* locus provides a rationale for unbiased genome-wide association studies to identify other risk-conferring SCAD loci and candidate genes (25).

It remains to be determined if SCAD susceptibility gene discoveries will translate into clinically-actionable genetic testing platforms to screen for major-effect variants that predict recurrence and/or risk in unaffected family members. Referral for formal genetic consultation can be considered, particularly in individuals with a family history of SCAD, aneurysms or dissections, or other features suggesting possible inherited connective tissue or syndromic conditions for which clinical genetic panels exist.

SEX HORMONES AND SCAD

Because the vast majority of patients affected by SCAD are women and SCAD constitutes an important cause of pregnancy-associated AMI (26), sex hormones have been implicated in the development of SCAD. Complicating the hormonal hypothesis, however, several large cohort studies have demonstrated that SCAD can affect women who are nulliparous, pregnant, postpartum, multiparous, and postmenopausal (3,5), and conclusive evidence is lacking regarding the use of exogenous hormones and the risk of SCAD or its recurrence. Notably, reported rates of contraceptive and postmenopausal hormone use in women with SCAD are not substantially different from the use in the general population (27,28). If hormones do play a role, it is unknown whether it is the absolute levels and/or fluctuations in circulating estrogen and progesterone that affect the process (29). Temporally, SCAD has been reported to occur just before or during menstruation while taking hormonal contraceptives and postmenopausal hormone therapy and in women with a history of infertility and/or prior or current treatment for infertility. Whether and by what mechanism the known effects

FIGURE 3 Coronary Artery Vasospasm Mimicking SCAD



Initial injection shows severe vasospasm of proximal right coronary artery **(A, arrow)**. This resolved with intracoronary nitroglycerin **(B)**, and closer inspection revealed a more subtle type 2 spontaneous coronary artery dissection (SCAD) of the distal posterior descending artery **(C, arrows)**.

of sex hormones on vascular, smooth muscle, and other tissues contribute to the risk of SCAD remains to be elucidated (1).

PREGNANCY-ASSOCIATED SCAD

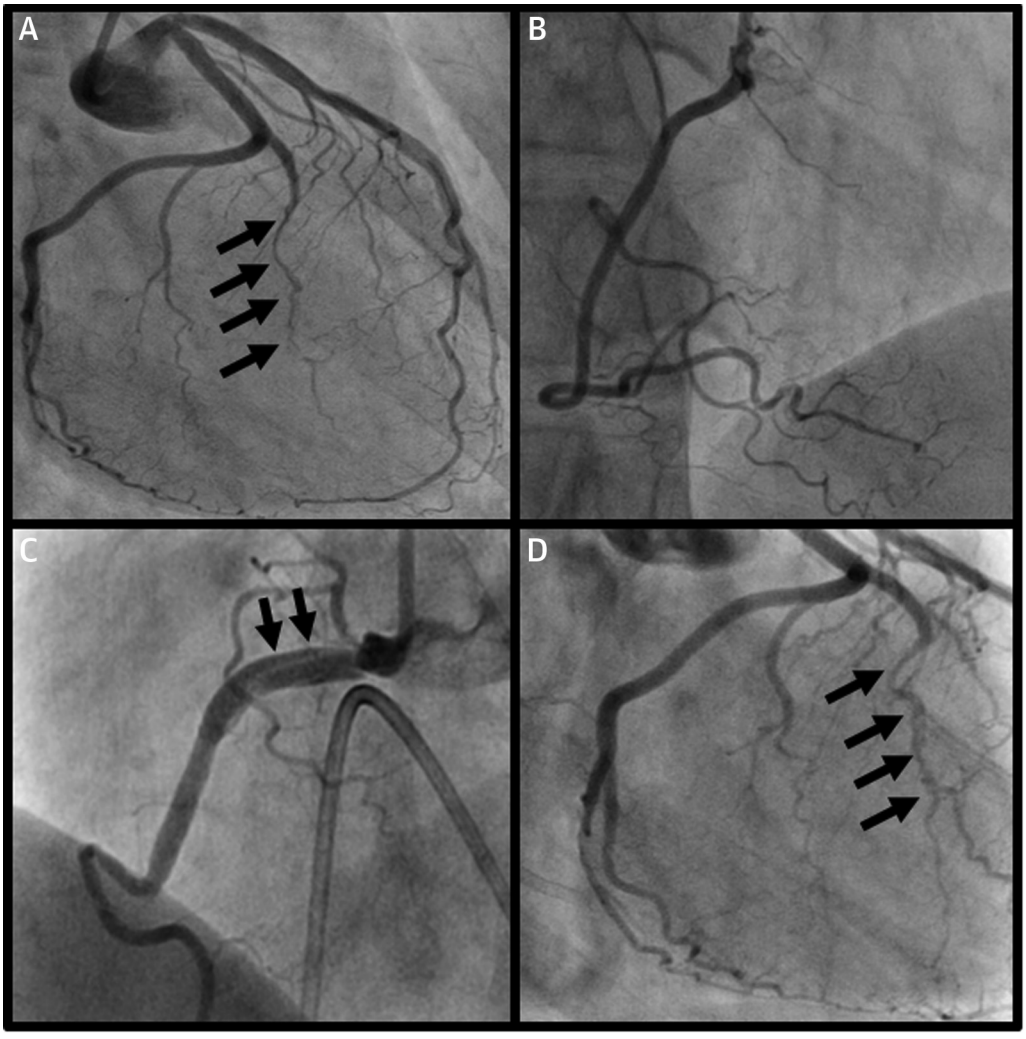
Pregnancy-associated spontaneous coronary artery dissection (P-SCAD) may occur at any time during or after pregnancy; the majority (>70%) occur postpartum, most commonly within the first week (30). Compared with those patients with SCAD not due to pregnancy, P-SCAD patients tend to have more severe clinical presentations with impaired left ventricular function, shock, left main, and multivessel dissections (30–34). P-SCAD comprises <5% to 17% of SCAD cases overall (5,7,10,35,36) and 14.5% to 43% of pregnancy-associated AMI (26,37), and is estimated to affect 1.81 per 100,000 pregnancies (38). Women with P-SCAD compared with non-P-SCAD women tend to be older at first childbirth and multigravidas; recurrent SCAD rates appear to be similar (**Table 2**) (30). Both P-SCAD and non-P-SCAD patients are more frequently multiparous and report a higher prevalence of prior infertility treatment and pre-eclampsia than U.S. reported data (30).

CLINICAL PRESENTATION AND DIAGNOSIS

PRECIPITATING FACTORS (TRIGGERS). In addition to pregnancy, a number of factors have been associated with onset of SCAD in as many as two-thirds of patients, most commonly extreme physical or emotional stress (5,35,36) (**Central Illustration**). Among SCAD patients reporting precipitants, emotional stressors appear more common in women, whereas physical stressors have been more often reported among men (35,39). Precipitants from isolated case reports, such as retching (36,40), cocaine exposure (41), or cancer treatment (42), may represent physical and/or emotional stressors. Notably, the frequency of patient-reported stressors prior to SCAD AMI is more than twice as high as in other ACS cohorts (40,43). Caution must be exercised before invoking causality for these associations due to the lack of objective data as to magnitude of the precipitant exposure and the effect of recall bias, especially because many SCAD studies utilize retrospective surveys (36,39,44).

CLINICAL PRESENTATION. The clinical presentation of SCAD is similar to that of atherosclerotic ACS, the primary difference being the patient phenotype. As such, education and awareness must be emphasized to minimize missed and delayed diagnoses of SCAD, as a strong index of suspicion is often lacking in this patient population. The vast majority of patients with SCAD report chest pain or equivalent symptoms and have elevated serial biomarkers and ECG findings consistent with ST-segment elevation or non-ST-segment elevation AMI. SCAD can also present with ventricular arrhythmias, cardiogenic shock, or sudden cardiac arrest. (45). Rare reports of coronary

FIGURE 4 **Iatrogenic Dissection in a Patient With SCAD**

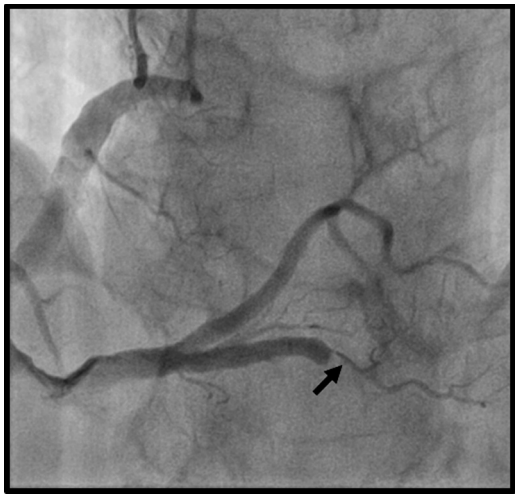


Spontaneous coronary artery dissection (SCAD) of the obtuse marginal (OM) coronary artery **(A, arrows)** with a normal right coronary artery (RCA) on the initial coronary angiogram **(B)**. In the post-procedure period, patient had new symptoms with ST-segment elevations on the electrocardiogram. She was found to have an iatrogenic right coronary artery dissection **(C, arrows)** and interval evolution of the OM SCAD **(D, arrows)**.

dissection diagnosed without accompanying biomarker and/or imaging evidence of myocardial necrosis (46) have raised the question of whether dissection may occur without infarction. Although possible, these cases may also represent patients with minimal or misinterpreted symptoms or who were not evaluated during the timeframe for biomarker detection of myocardial injury.

CATHETER-BASED CORONARY ANGIOGRAPHY. Coronary angiography is the primary and often the only modality necessary for experienced interventional cardiologists to diagnose SCAD and should be performed when possible in the setting of ACS. SCAD has a predilection for the mid-to-distal coronary arteries with the left anterior descending coronary artery most commonly affected. The Yip-Saw classification (**Central Illustration**) has helped to increase awareness of the variety of SCAD angiographic appearances. Unlike dissections in the setting of plaque rupture, the majority of SCAD present with type-2 appearances characterized by a long smooth narrowing, often tapering distally, either with distal reconstitution of a normal vessel or extending into the terminal branches. A small proportion mimic

FIGURE 5 Spontaneous Coronary Artery Dissection and Coronary Ectasia



Dissection of the posterior descending coronary artery **(arrow)** in a patient with coronary ectasia. It is unclear if the dissection is a consequence of the ectasia leading to endothelial-intimal disruption (akin to dissections associated with ulcerated atherosclerotic plaque) or whether both the ectasia and SCAD part of the same arteriopathy.

atherosclerotic stenosis (type 3). The appearance of coronary tortuosity and lack of intraluminal thrombus are also clueing that favor SCAD (47,48). The presence or absence of intimal dissection may also provide a clinically useful means to stratify risk. Along with multivessel SCAD involvement and severe stenosis (>80%), isolated intramural hematoma (IMH) confers a significantly higher risk of acute clinical deterioration after conservative management compared with presence of intimal dissection (14).

CHALLENGING DIAGNOSES: ROLE OF INTRAVASCULAR AND NONINVASIVE IMAGING

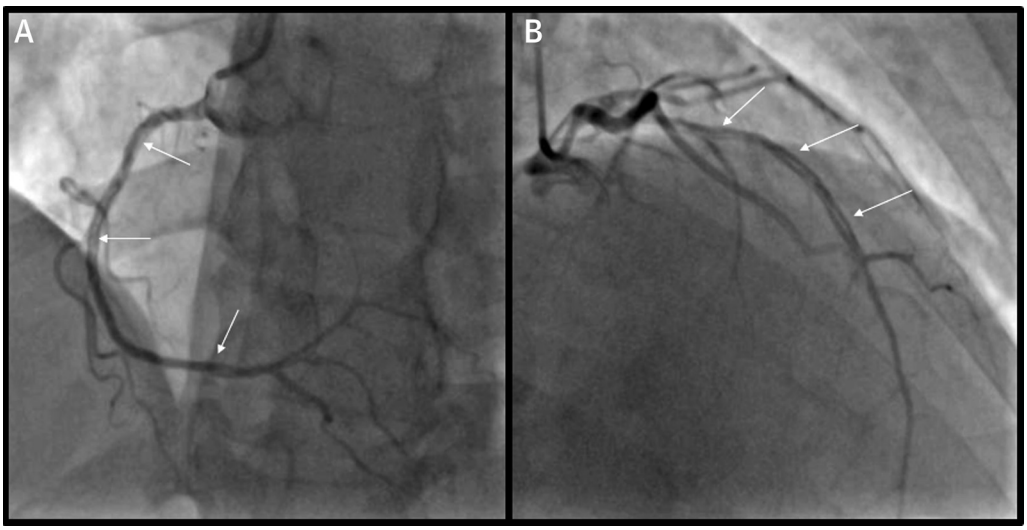
Some SCAD defy straightforward classification, including hybrid cases (e.g., a long type 2 appearance with a very short type 1 focus of contrast extravasation), distal coronary occlusions mimicking coronary embolism (type 4 appearance) (2), or left anterior descending coronary SCAD with Takotsubo-like ventricular appearances (49,50). As clinical awareness of SCAD has increased, the authors of this review have observed that an SCAD diagnosis may be assigned even in cases where angiographic findings were not "diagnostic." Subsequent diagnoses of myocarditis, coronary vasospasm, atherosclerosis, thromboemboli, and microvascular disease have been made, with important short- and long-term implications for patients. **Figures 2 to 9** provide angiographic examples that may challenge even the most experienced operators. Administration of intracoronary nitrates, intracoronary imaging, when safe and available, and/or follow-up noninvasive or invasive coronary imaging may help distinguish SCAD from other etiologies.

Whereas OCT images in SCAD are characteristic, IVUS images require closer scrutiny to discriminate between disrupted plaque and SCAD, given the lower spatial resolution of IVUS. Coronary anatomy in SCAD may reduce the safety of intracoronary imaging (e.g., severe tortuosity, small lumen size, distal lesion) (17). Given that angiographic diagnosis is possible in most cases of SCAD and conservative management is favored, coronary instrumentation for intracoronary imaging is best reserved for cases of diagnostic uncertainty or where percutaneous coronary intervention (PCI) is required. When imaging is required, limiting assessment to the most proximal segment of the hematoma may minimize the risk of complications.

For persistent diagnostic uncertainty after angiography, ancillary diagnostic testing can be employed. Cardiac magnetic resonance (CMR) imaging showing delayed gadolinium enhancement in a territory corresponding to a suspected dissection can help confirm SCAD or suggest an alternate diagnosis (e.g., myocarditis) (**Figure 10**), but a normal CMR does not exclude SCAD. A substantial minority of patients with angiographically-confirmed SCAD do not have CMR evidence of infarction. In one series, CMR was normal in 39% (performed median 423 days after SCAD) (34) and in 11% (2 of 18) in another series imaged within 8 days of SCAD, including a patient with left main dissection presenting with sudden cardiac arrest (46).

Noninvasive cardiac computed tomography angiography (CTA) has been utilized both in the initial diagnosis of SCAD and to assess healing; however, cardiac CTA diagnostic criteria for SCAD need further refinement. During the acute SCAD episode, dissection planes are infrequently identified (<15%) by cardiac CTA; abrupt luminal changes and sleeve-like hematomas within the coronary artery wall are more often observed (51,52). Limitations of cardiac CTA include low spatial resolution for small vessels, motion artifact, and unknown sensitivity and specificity. A coexistent arteriopathy such as fibromuscular dysplasia (FMD) may help to solidify an SCAD diagnosis due to its high prevalence among those with SCAD, although only after other etiologies such as

FIGURE 6 Persistent Dissection Versus Recanalized Thrombus



Multiple parallel channels in the right coronary artery **(A, arrows)** and the left anterior descending coronary artery **(B, arrows)**. This may represent a chronic form of type 1 dissection, recanalization of thrombus, or another process.

atherosclerosis are excluded (51,53). In select cases where the benefit of accurate diagnosis outweighs risks, repeat angiography may be useful.

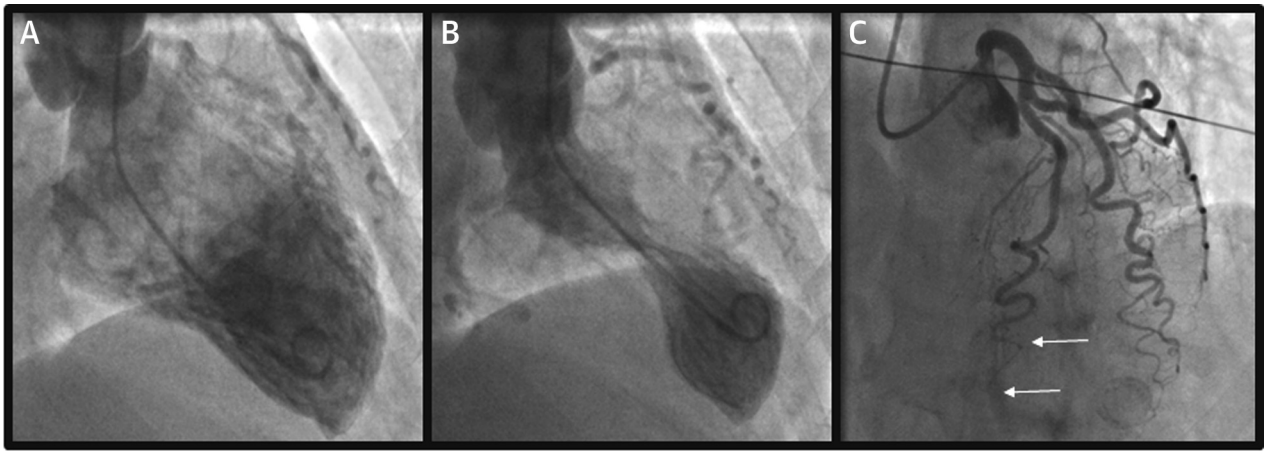
ACUTE MANAGEMENT

The goal of management in the acute phase is to restore or preserve myocardial perfusion and cardiac function. Adverse outcomes related to thrombolytic use in SCAD due to extension of dissection or hematoma have been reported (54), so in this context, thrombolysis is generally not recommended. If SCAD occurs during a pregnancy, the management strategy is similar to the nonpregnant state, with additional considerations to optimize maternal and fetal outcomes (**Table 3**). Although some advocate for avoidance of diagnostic coronary angiography in stable pregnant women with MI (32), this is often driven solely by fetal radiation concern. In light of substantial maternal mortality rates (37) and negligible fetal radiation exposure with proper shielding, adherence to standard of MI care among pregnant women is advised (55).

PERCUTANEOUS CORONARY INTERVENTION. PCI is the mainstay of guideline-based revascularization for ACS, but compared with atherosclerotic AMI, the outcomes of PCI in SCAD are less predictable with higher rates of complications and suboptimal outcomes (1,2,4,48), including an elevated risk of iatrogenic dissection and abrupt vessel occlusion (56) (**Figure 11**). Hematoma propagation (**Figure 12**) occurs in up to one-third of PCI cases, frequently requiring the use of multiple unplanned stents (48). Subsequent resorption of the hematoma may lead to late strut malapposition (**Figure 13**). Because the majority of conservatively managed SCAD recover normal coronary architecture, often within 30 days, most interventionalists adhere to an "as conservative as possible" approach to revascularization (**Figure 14**) (1). In a review of SCAD patients who underwent repeat coronary angiography for a variety of indications, among those who were imaged ≥30 days post-SCAD, 95% showed angiographic healing (57). When a SCAD diagnosis is clear, there is minimal ongoing ischemia, and coronary involvement is distal or with preserved coronary flow, additional coronary instrumentation should be avoided. A recent prospective observational series of 750 cases reported 84.3% of cases were managed nonoperatively (5), suggesting that in experienced centers, most SCAD cases can be managed conservatively.

Compared with the approach in atherosclerotic ACS, in SCAD the focus should be less on restoring normal coronary architecture and more on the minimal measures required to restore TIMI (Thrombolysis In Myocardial Infarction) flow grade 3. Recent attention has shifted to developing new metrics for what constitutes PCI "success" because revascularization remains an important management requirement for a minority of SCAD patients, such as those with

FIGURE 7 SCAD Mimicking Stress Cardiomyopathy (Takotsubo)

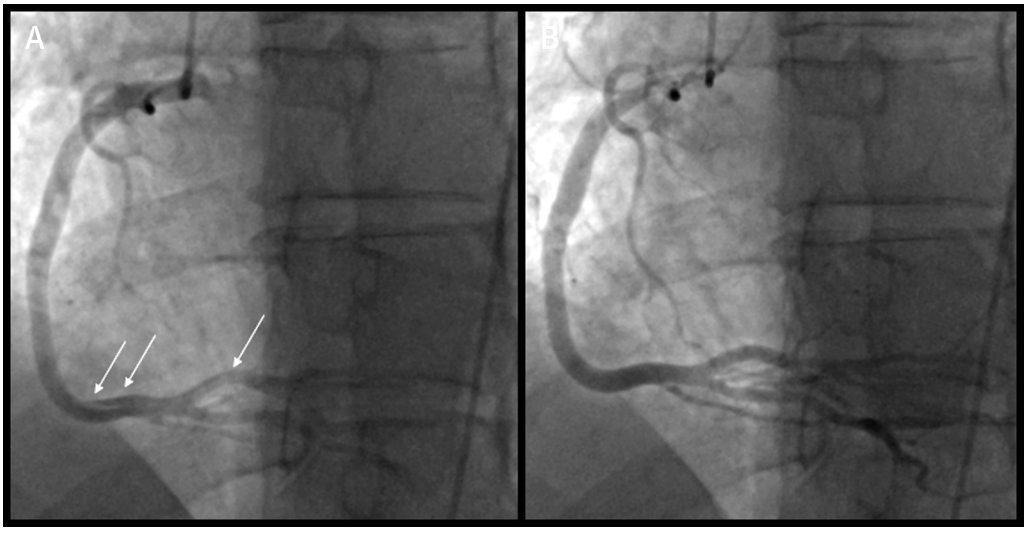


Typical Takotsubo-like left ventricular angiography with basal hypercontractility and apical sparing **(A and B)**. Tortuous coronary tree with type 2b SCAD in SYNTAX segment 8 **(C, arrows)**. SCAD = spontaneous coronary artery dissection; SYNTAX = Synergy Between PCI with TAXUS and Cardiac Surgery

proximal coronary occlusions, those with unstable rhythm and/or hemodynamics, and those who progress to occlusion after initial conservative management (1,14). A number of techniques have been advocated to minimize hematoma propagation, but there is minimal comparative outcome data (2). These include small-diameter balloon angioplasty, cutting balloon or appropriately sized standard balloon angioplasty aimed at fenestrating and depressurizing the false lumen, proximal and distal-edge stenting, and use of bioresorbable scaffolds.

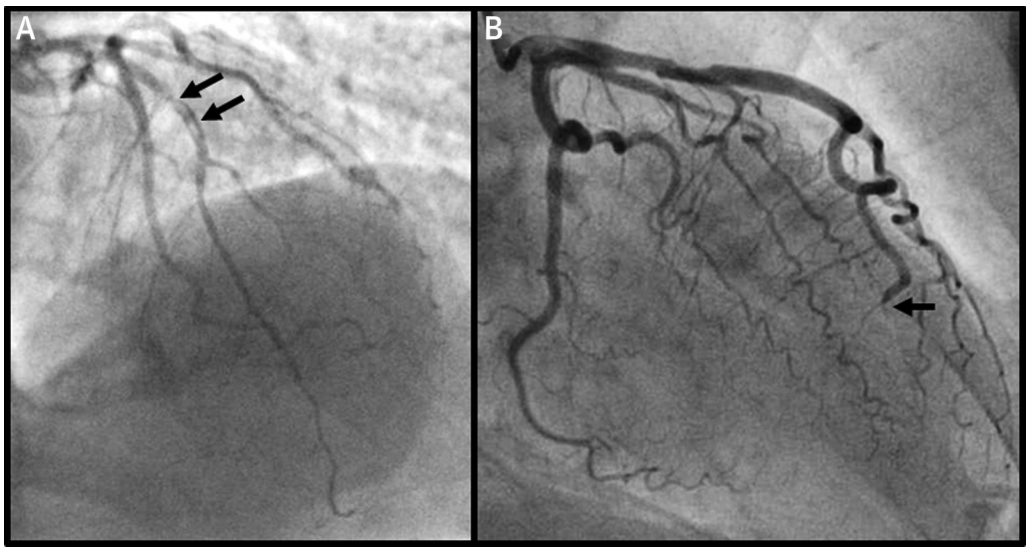
CORONARY BYPASS GRAFTING. Coronary artery bypass grafting (CABG) is usually reserved for situations where PCI either has failed or is considered

FIGURE 8 Pseudo-Dissection



Streaming of contrast in the right coronary artery **(A, arrows)** can mimic spontaneous coronary artery dissection. The artefact disappears with complete filling of the vessel **(B)**.

FIGURE 9 **Ruptured Atherosclerotic Plaque Mimicking Spontaneous Coronary Artery Dissection**



Localized stenosis at the septal artery take-off **(A, arrows)** is followed by a linear filling defect that could be due to atherosclerotic dissection or plaque-associated thrombus with the appearance of a type 1 dissection. The differential diagnosis in **B** is dissection **(arrow)** or atheroembolism due to upstream plaque rupture, thrombosis, and downstream thrombus embolization. In these cases, use of intracoronary imaging, coronary computed tomographic angiography, or other ancillary diagnostic techniques may be required.

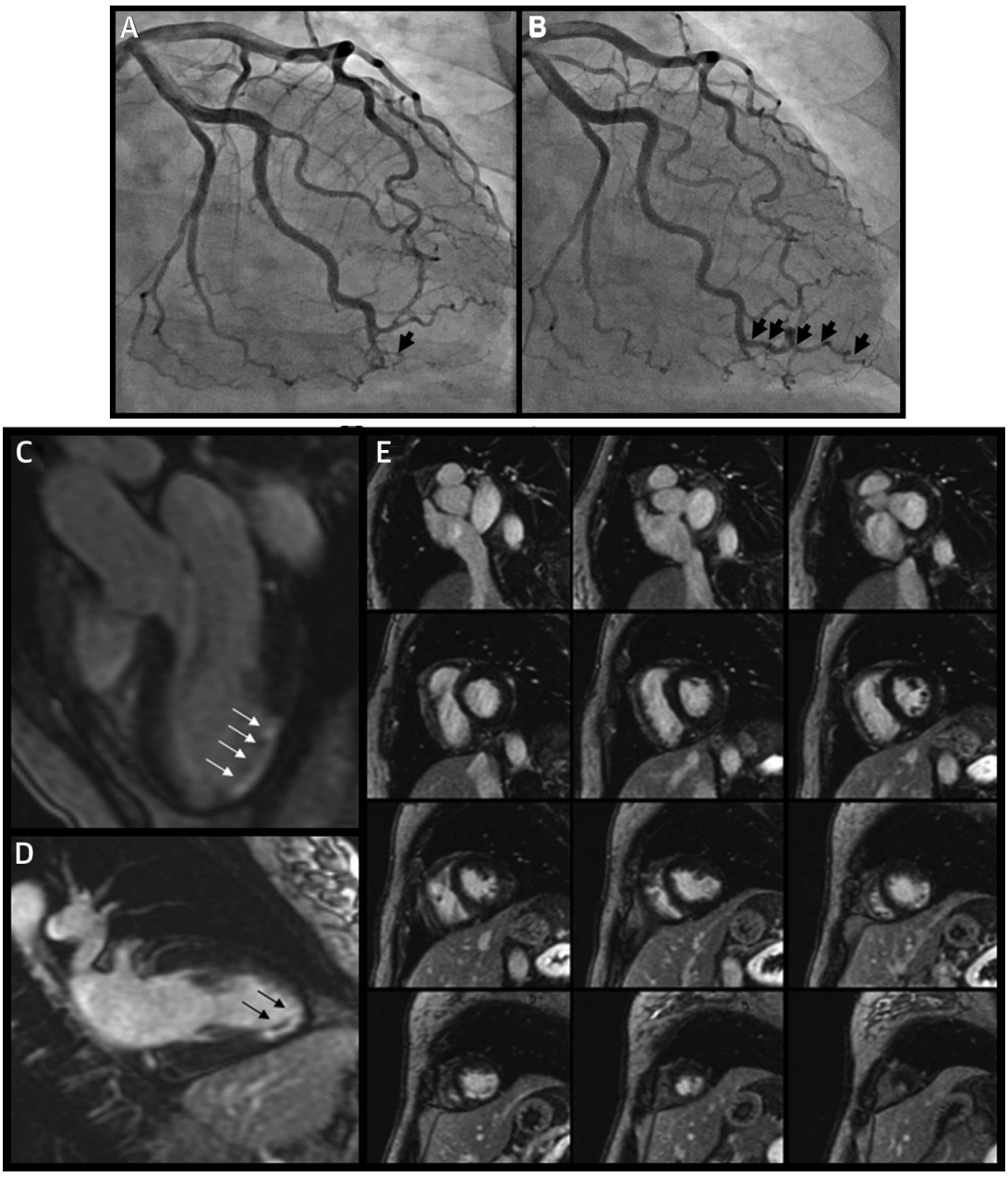
extremely high risk (e.g., left main stem dissections with ongoing ischemia/infarction). In addition to the risks associated with performing surgical procedures during AMI, SCAD-specific technical concerns include the fact that dissected coronary artery tissues are profoundly fragile, unlikely to hold suture, and prone to anastomotic complications. This may be further exacerbated in patients with hereditary connective tissue disorders. Surgeons generally try to avoid attempts to bypass onto dissected tissue directly, and therefore, patients with SCAD extending into the distal vessels may not be good candidates for CABG.

Tweet et al. (48) examined the outcomes of 20 patients who underwent CABG for SCAD. Although the early mortality was significant at 5%, there was no further mortality at 5 years. This was despite the fact that only 5 of 16 bypass grafts remained patent at a median follow-up of 3.5 years. Healing of the native coronary arteries results in increasing competitive flow and contributes to high rates of bypass conduit failure. Regardless, these observations should not exclude CABG, as it can be an effective temporizing measure to reduce serious clinical complications while the vessel heals. Patients undergoing CABG have been observed to have similar 5-year event rates compared with those treated conservatively (48). Because there is no evidence for arterial versus venous grafting and given the discordance between a long-term graft patency and survival, the use of the reliable and immediately high-flow venous conduits seems a reasonable choice, particularly for unstable patients with large territories of myocardium at risk.

POST-PROCEDURAL MANAGEMENT. Differentiating ischemic and nonischemic etiologies of early post-SCAD chest pain remains a major challenge. Although early reinfarction does occur (incidence: 6.1% to 17.5% with the majority occurring pre-discharge) (5,14), most chest pain is nonischemic. Given the iatrogenic dissection risk (56), the focus of management is on relieving symptoms with optimal medical therapy (e.g., blood pressure control, anti-anginals, analgesia), identifying patients where invasive reinvestigation is mandatory (e.g., those with evidence for progressive ischemia or hemodynamic instability), and avoiding invasive angiography where possible.

The increasing adoption of conservative revascularization strategies in SCAD with the potential for late hematoma extension, coupled with the frequent complexity of PCI, support consideration of a longer period of in-hospital observation after SCAD. A recent prospective study reported a post-discharge major adverse cardiac events (MACE) rate of 2.7% in the 30 days following a median 4-day length of stay (5).

FIGURE 10 **Nondiagnostic Coronary Angiography/Missed Spontaneous Coronary Artery Dissection**



The initial coronary angiogram was reported as "normal" **(A)**. However, subsequent cardiac magnetic resonance imaging showed delayed gadolinium enhancement consistent with an inferolateral wall infarction **(C, D, E, arrows)**, prompting a review of the angiogram and identification of a distal obtuse marginal occlusion **(A, arrow)**, which was healed on a repeat coronary angiogram **(B)**. This patient also had diffuse fibromuscular dysplasia, which included involvement of the left internal mammary artery **(F)** and right renal artery **(G)**.

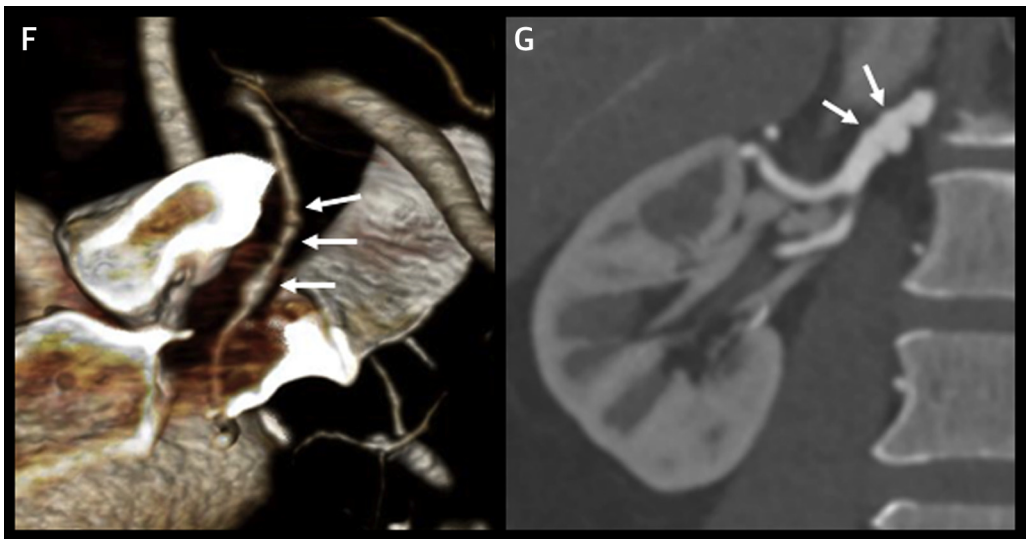
Continued on the next page

These data support individualized length of stay according to perceived risk but erring toward longer admission than for uncomplicated atherosclerotic ACS.

MEDICAL THERAPY AFTER SCAD

The goal of medical therapy for SCAD is relief of symptoms and prevention of immediate

FIGURE 10 Continued



complications and recurrent SCAD. Although there are no randomized controlled trials to guide SCAD-specific pharmacological management, individuals with left ventricular dysfunction should be treated according to standard heart failure guidelines with beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (1,58), and those receiving stents should be treated according to guidelines for PCI management (59). Beta-blocker therapy, if tolerated, can be justified based on a retrospective study in which its use was associated with lower rates of SCAD recurrence (60), but this observation has not been validated in other cohorts (61). Hypertension has been associated with recurrent SCAD and should be treated (60). The pathophysiology of SCAD versus atherosclerotic AMI should inform the use of most other "standard" or guideline-base therapies. For instance, there is no evidence that hyperlipidemia is relevant to the pathophysiology of SCAD recurrence risk (60). Lipid-lowering therapy is therefore usually reserved for patients who have hyperlipidemia or whose risk profile would warrant treatment according to primary prevention guidelines (62). Although early inpatient anticoagulation may provide benefit by reducing thrombus burden, there are also theoretical concerns of accentuating bleeding into the IMH leading to extension of the dissection. The general approach is to discontinue systemic anticoagulation and glycoprotein IIb-IIIa inhibitors once SCAD is diagnosed unless there is apparent intraluminal thrombus or other indications for systemic anticoagulation (1).

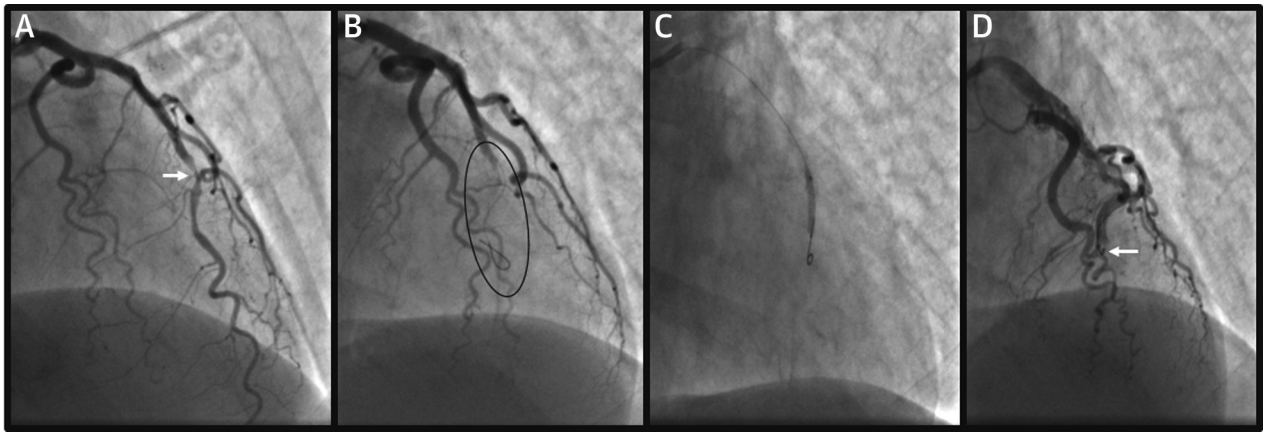
Patients who undergo PCI should receive standard guideline-based dual antiplatelet therapy (DAPT) (59). For conservatively managed (no PCI) patients, there is a lack of consensus on the use and duration of aspirin alone or DAPT, because the pathophysiological mechanisms in SCAD are distinct from atherosclerotic ACS and the presence of true luminal thrombus in acute SCAD is uncommon (17,48). Current guideline-based therapy for ACS recommends DAPT for 1 year and lifelong aspirin (59), and some authors have advocated for following these guidelines in SCAD. However, others limit or avoid the use of early or prolonged DAPT in light of lack of evidence for benefit, infrequent intracoronary thrombus, the potential for bleeding within the IMH causing dissection extension, and the documented elevated major and minor bleeding risks, even with low dose aspirin monotherapy (63). Until outcomes data are available, a reasonable approach we have employed is

TABLE 3 Management of SCAD in the Pregnant Patient

After 20 weeks gestation, utilize left lateral recumbent positioning whenever possible to reduce aortocaval compression and optimize venous return.
Consider continuous fetal monitoring at/beyond gestational age of fetal viability (~≥23 0/7 weeks) during the acute SCAD episode (98).
Dependent on gestational age, consider antenatal corticosteroids if pre-term delivery is anticipated within 7 days.
If delivery cannot be delayed the recommended 2+ weeks after late third trimester (≥34 weeks gestation) SCAD, consider maternal stabilization and optimization of cardiac status followed by planned delivery under controlled conditions (management decisions individualized by the multidisciplinary team).

SCAD = spontaneous coronary artery dissection.

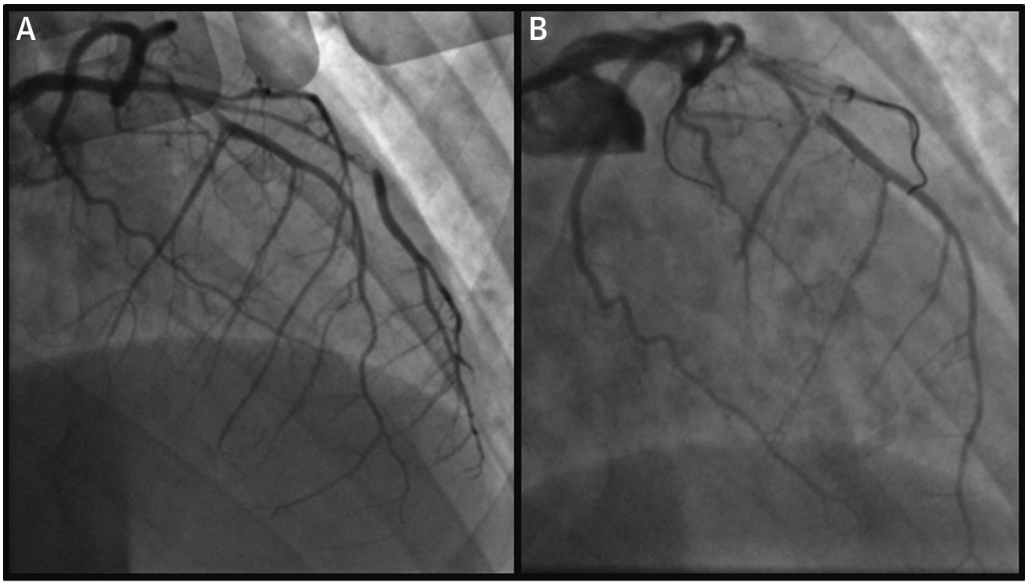
FIGURE 11 Percutaneous Intervention Into a False Lumen of SCAD



SCAD of the mid-left anterior descending artery with normal distal flow **(A, arrow)**. There was loss of flow with wire advancement **(B, oval)** with subsequent balloon angioplasty in the false lumen **(C)** and further intimal separation with a persistent lack of coronary flow **(D, arrow)**. SCAD = spontaneous coronary artery dissection.

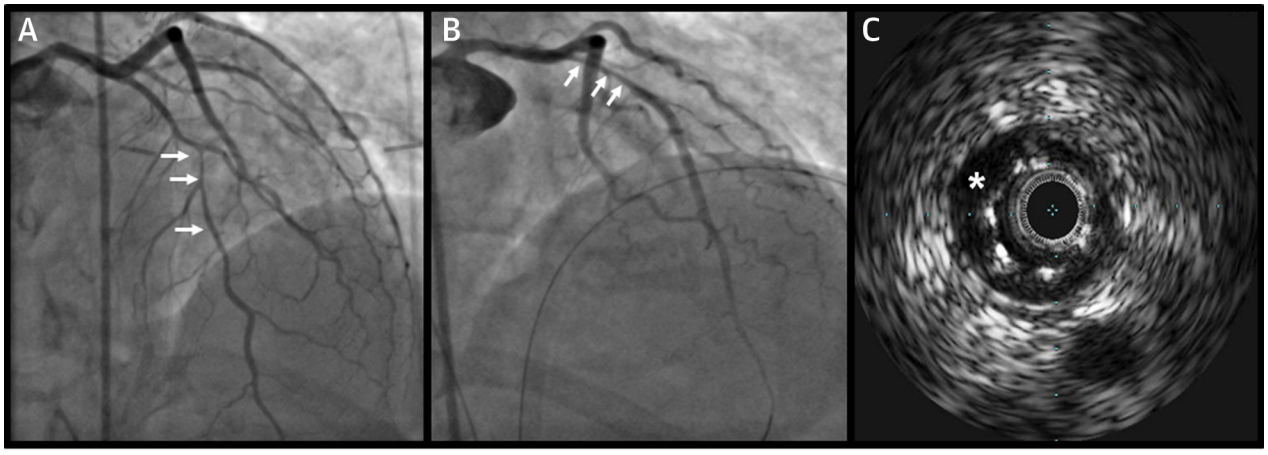
to recommend DAPT for at least 2 to 4 weeks after SCAD and then continue low-dose aspirin alone for a total of 3 to 12 months, encompassing the timeframe for SCAD healing. In individuals at higher risk of bleeding events, consideration of aspirin alone or no antiplatelet therapy is not unreasonable. Decisions about longer-duration antiplatelet therapy after conservatively managed SCAD should incorporate comorbidities, including the presence of FMD or other dissections, for which expert consensus

FIGURE 12 Hematoma Propagation



Severe, multivessel, pregnancy-associated spontaneous coronary artery dissection **(A)** with subsequent hematoma extension into the left main **(B)** and loss of flow to the left anterior descending coronary artery requiring emergency coronary artery bypass grafting.

FIGURE 13 Strut Malapposition



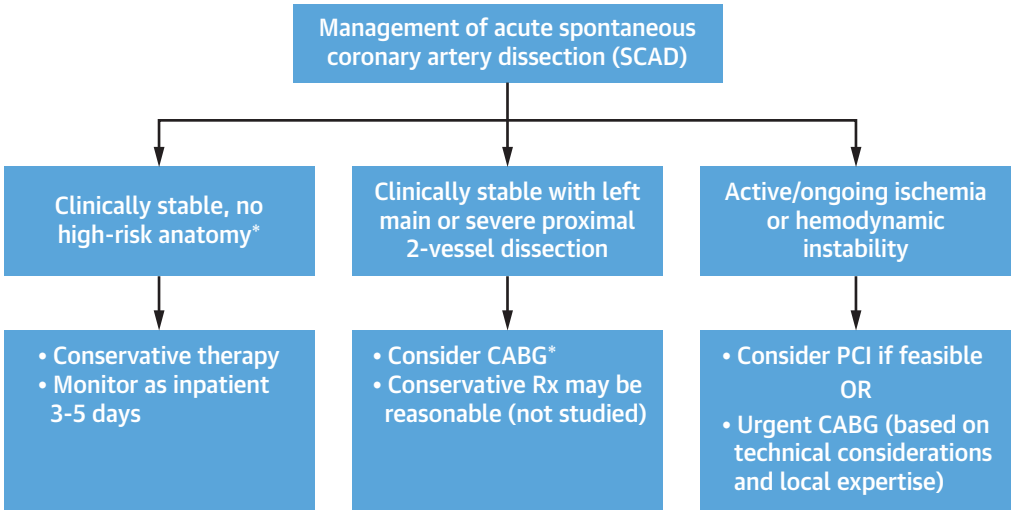
The left anterior descending coronary artery **(A, arrows)** treated with stent placement and proximal displacement of hematoma **(B, arrows)**. Intravascular ultrasound shows an underdeployed stent **(C, asterisk)**.

indicates low-dose aspirin as "reasonable," acknowledging the lack of clinical trial data to support the recommendation (64). Shared decision-making should be employed, especially among women who experience more frequent and more serious bleeding complications related to aspirin use (65,66).

SUBSEQUENT CARE AND MANAGEMENT OF CHEST PAIN

The outpatient evaluation after SCAD should be individualized and depends upon the clinical status, the extent and location of the dissection and

FIGURE 14 Algorithm for Management of Acute SCAD



Although a "conservative as possible" approach is generally preferred in acute SCAD, more severe presentation, ongoing symptoms, and other high-risk feature may warrant revascularization. *Left main or proximal 2-vessel coronary artery dissection. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; Rx = management. Adapted with permission from Hayes et al. (1).

TABLE 4 Outpatient Evaluation After Spontaneous Coronary Artery Dissection

Clinical Visit After SCAD
History of recent illness
Details of SCAD presentation, diagnosis, and management
Description of possible precipitants such as emotional stressors, physical activity, medications, illicit drug use, illness, and so on
Participation in cardiac rehabilitation
Status of mental health and support system
Personal medical history
Prior myocardial infarctions, cardiovascular diagnoses
Presence of fibromuscular dysplasia or other arterial abnormalities
Migraine
Connective tissue disorder diagnoses or signs/symptoms
Reproductive history
Number of pregnancies and deliveries
Pregnancy/delivery mode, outcomes and complications (e.g., pre-eclampsia, hypertension in pregnancy, diabetes, and so on)
Infertility and infertility treatment
Sex hormone use history
Rheumatologic/autoimmune disorders
Atherosclerotic risk factors
Family history
Premature myocardial infarction or stroke, sudden unexpected or cardiac death
Arterial abnormalities such as aneurysms, dissections, and fibromuscular dysplasia
SCAD
Connective tissue disorders
Social history
Presence of adequate psychosocial support system
Barriers to cardiac rehabilitation participation
Employment, jobs, roles, and leisure time activities that might be affected by SCAD diagnosis
Diet and exercise patterns (pre- and post-SCAD)
Tobacco, alcohol, or illicit drug use
Physical examination. In addition to a usual examination, focus on:
Cardiopulmonary examination
Vascular examination including palpation and auscultation for carotid, renal, abdominal aortic, and femoral artery bruits
Palpation and assessment of prior arterial access site (e.g., radial artery)
Assessment of skin integrity, hyperflexibility, (Beighton score), bifid uvula

SCAD = spontaneous coronary artery dissection.

myocardial injury, and symptoms. However, there are some key components of patients' recent and past history, family history, and physical and diagnostic evaluation to consider when assessing an SCAD outpatient (**Table 4**).

Post-SCAD chest pain is common, and may occur early and continue for many months. Rehospitalization and reinvestigations are frequent (67); a proposed approach to assessment and management is shown in **Figure 15** (1). Symptoms may vary from those of the index SCAD, may be nonexertional, may occur with mental stress or in the perimenstrual period, and are sometimes nitrate responsive, despite the absence of fixed coronary obstruction or inducible ischemia on functional testing. Given the risk of iatrogenic catheter-induced dissection in SCAD (56), careful consideration is required before recourse to invasive angiography. Acutely, this may include serial ECG and biomarker measurements and, if stable, cardiac CTA (with stent subtraction as required) or functional imaging (e.g., stress echocardiography or perfusion imaging). Effective antianginal therapy may be limited by symptomatic hypotension and migraine headaches (3,36), often limiting tolerance of nitrate therapy. Overall response to antianginal therapies is variable, but most affected patients improve over time, whether due to improvement in the underlying pathology, reduction in anxiety, or both. If there are persistent, concerning symptoms or uncertainty regarding the diagnosis after noninvasive assessment, cautious invasive coronary angiography by an interventionalist familiar with SCAD and mindful of the iatrogenic dissection risk may be indicated.

EARLY POST-SCAD IMAGING

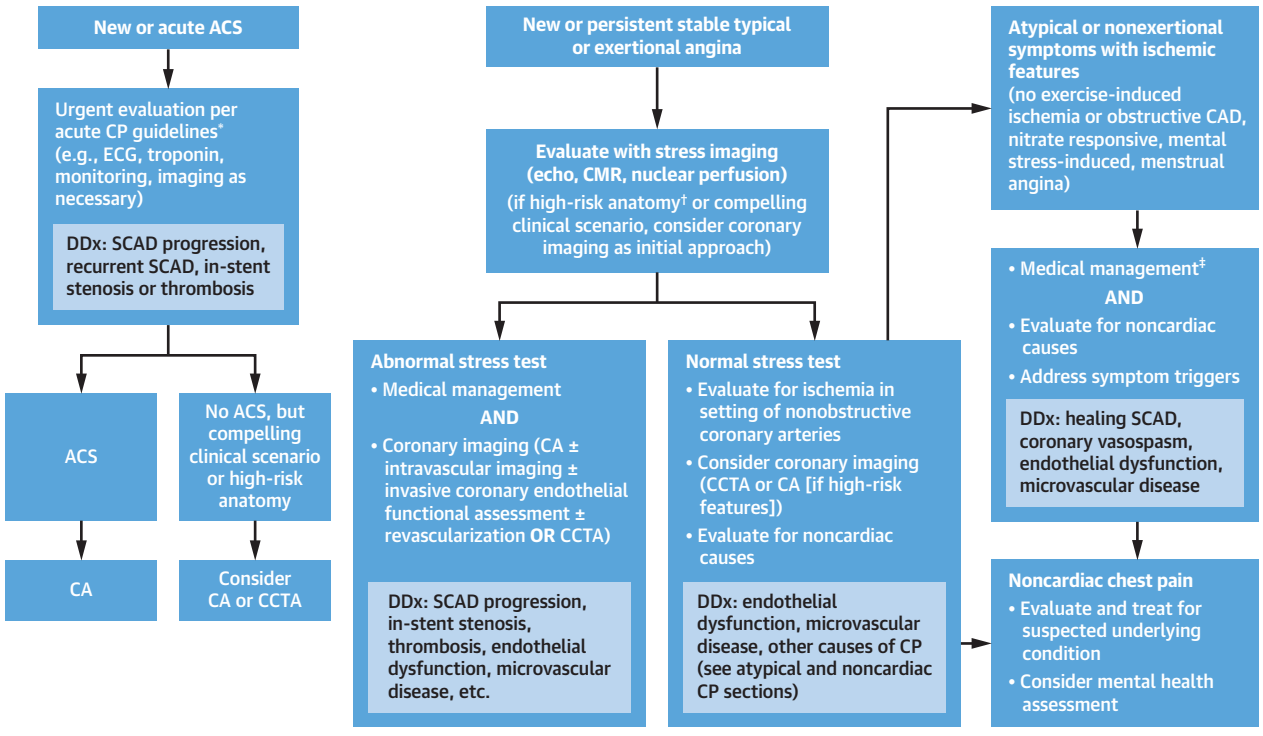
Although patients presenting with ST-segment elevation MI, proximal or multivessel SCAD, TIMI flow grade 0/1, P-SCAD, or connective tissue disorders tend to have larger infarctions that may result in severe left ventricular dysfunction, the extent of myocardial damage associated with SCAD is commonly quite limited (34). Reassessment of cardiac function at 3 months is appropriate for those with reduced left ventricular function at the time of AMI. Routine invasive angiography in asymptomatic patients after SCAD is not recommended due to the risk of iatrogenic dissection coupled with the high rates of healing of conservatively managed SCAD (57). Among medically managed patients with proximal-to-mid vessel dissections, there may be a role for cardiac CTA imaging to confirm healing, particularly for type 1 dissections or when cessation of antiplatelet therapies is being contemplated (68). Cardiac CTA imaging of smaller caliber mid-to-distal dissections is often limited by inadequate spatial resolution or challenges of stent subtraction. Additional radiation exposure among this younger patient population and the risk of false-positive findings driving invasive investigations should also be considered (69,70).

LONG-TERM MANAGEMENT AND OUTCOMES

ASSESSING FOR CONCURRENT ARTERIOPATHIES.

SCAD may be the initial manifestation of an underlying systemic arteriopathy. A 2005 case series first reported the presence of multifocal renal artery FMD in 7 women who presented with ACS, most of whom had SCAD using contemporary criteria (71). Two large series published in 2012 (35,72) confirmed the association of SCAD and FMD, and since then, multiple

FIGURE 15 Evaluation and Management of Chest Pain After Spontaneous Coronary Artery Dissection



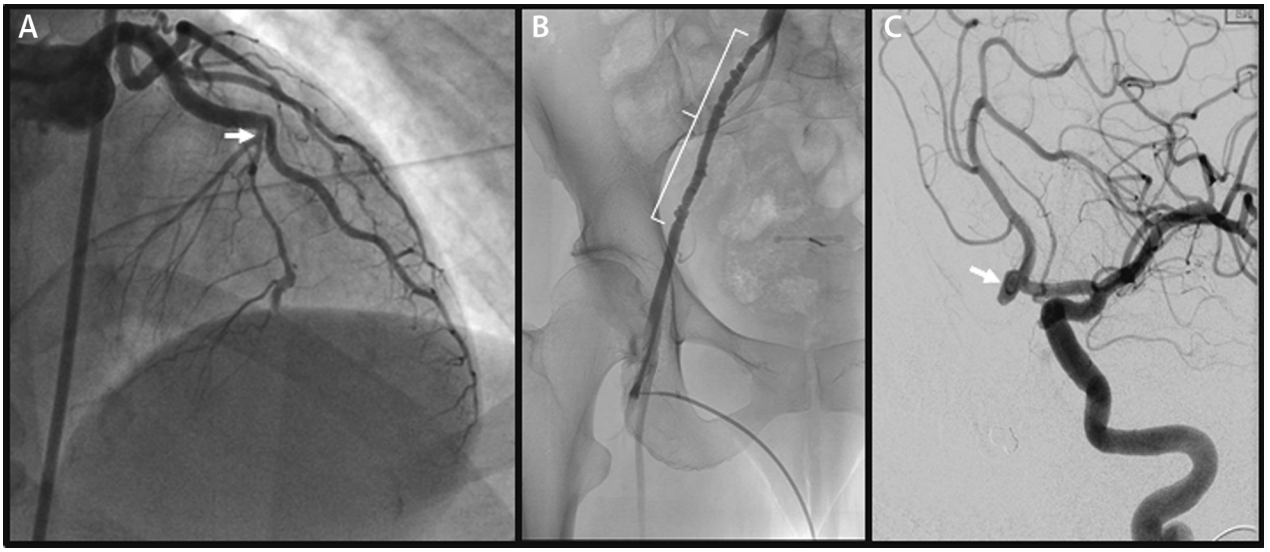
Chest pain syndromes are common both early and late after SCAD. The algorithm provides an approach to evaluation and management based on the acuity and the nature of the symptoms, prioritizing accurate diagnosis and relief of symptoms while minimizing risk of iatrogenic harm. *Current guidelines. †SCAD affecting the left main or 2 proximal coronary arteries. ‡Long-acting nitrates, calcium-channel blockers, or ranolazine. Reprinted with permission from Hayes et al. (1). ACS = acute coronary syndrome; CA = coronary angiography; CAD = coronary artery disease; CMR = cardiac magnetic resonance; CP = chest pain; CTA = computed tomography angiography; DDx = differential diagnosis; Echo = echocardiography.

other studies have reported extracoronary vascular abnormalities (EVAs), most commonly FMD (**Figure 16**), in patients with SCAD (3,5-7,47,48,60,73). Associations of coronary arterial FMD and SCAD have also been reported in autopsy case reports (74-76) and intravascular imaging using OCT has demonstrated abnormal coronary arteries in patients with FMD (77). The largest cohorts reported multifocal FMD in >50% overall and head/neck aneurysm and pseudoaneurysm in 7% to 11% (**Table 5**). The association of SCAD with coronary arterial tortuosity (47) as well as dissection, aneurysm, or pseudoaneurysm in up to one-quarter of patients who do not otherwise have clinical evidence of FMD raises the question as to whether these represent a distinct or overlapping arteriopathy or a subtle form of FMD that is not detected by current diagnostic techniques (64).

Recognizing the high coprevalence and potential implications for surveillance and treatment of EVA in patients with SCAD, the major consensus documents on SCAD and FMD recommend arterial imaging from head to pelvis, usually with noninvasive cross-sectional imaging with CTA or magnetic resonance angiography (1,58). Some clinicians have questioned the rationale for imaging, asserting that identifying FMD may be unduly alarming to patients, especially because it may have no bearing on prognosis, treatment, or outcomes. As such, it is important to clearly articulate the goals of arterial screening as not simply "diagnosing FMD" but identifying clinically important vascular complications that warrant treatment or longitudinal follow-up.

Although data are admittedly sparse on the clinical impact of screening for EVAs in patients with SCAD, among patients with FMD, there are more data to support the rationale for EVA screening. This includes findings of intracranial aneurysm in 12.9% of 669 imaged FMD patients, among whom >40% (32 of 74) had aneurysm measurements of >5 mm (78,79). Practice-changing arteriopathies are most frequently

FIGURE 16 Spontaneous Coronary Artery Dissection and Systemic Arteriopathy



Dissection of the mid LAD (**A, arrow** marks beginning of dissection) with complete occlusion in a patient presenting with anterior STEMI. Catheter based angiography in the same patient reveals the classic beading of multifocal fibromuscular dysplasia **(B, bracket)** in the right external iliac artery and a 6-mm anterior communicating artery aneurysm **(C, arrow)**.

identified in the intracerebral and cervical vascular beds and chest imaging has a substantially lower yield for EVA than imaging of other vascular beds (58,73). The relevance of these findings may be greater for women who are pregnant or contemplating pregnancy. Whether the detection of EVA in patients with SCAD has an impact on subsequent events (e.g., recurrent SCAD or other dissections, aneurysm growth or rupture) or efficacy of procedures to prevent such events remains unknown and should be an active area of future study.

RECOMMENDATIONS FOR PHYSICAL ACTIVITY AFTER SCAD

The onset of SCAD symptoms has been correlated with physical activity in up to 32% (5,7,30,80). Reported activities have included aerobic and isometric exercises and both newly initiated and usual exercise routines. Fear and hesitancy regarding physical activity after SCAD are common and often lead patients to curtail or avoid physical activity altogether. Some clinicians continue to advise highly restrictive physical activity parameters despite a lack of evidence for protection from recurrent SCAD and the potential to cause harm (e.g., deconditioning, mental health decline, weight gain, osteopenia). Cardiopulmonary exercise contributes substantially to overall physical and mental health, and studies among SCAD patients in cardiac rehabilitation have demonstrated overall benefit and safety; therefore, pursuing regular, moderate exercise likely outweighs the theoretical risks of recurrent SCAD (1,2,81). Most SCAD patients, especially those with recurrence or noncoronary aneurysms or dissections, should avoid extreme endurance training, exercising to exhaustion, elite competitive sports, or vigorous exertion in extremes of ambient temperature. Additionally, patients should avoid lifting or carrying heavy objects that require straining or prolonged Valsalva. Setting specific weight limits for lifting or exercise heart rate or duration is often counterproductive and frustrating, because patients have varying baseline aerobic capacities and strength that often change over time with conditioning, medications, and other factors. Recommendations should to be tailored to the individual using the general principles outlined in the previous text and may be best determined during participation in cardiac rehabilitation (1,2).

PSYCHOSOCIAL/MENTAL HEALTH CONSIDERATIONS

Incident cardiovascular disease and SCAD in particular are associated with high levels of psychological distress, including depression, anxiety, and post-

TABLE 5 Prevalence of Extracoronary Vascular Abnormalities and Fibromuscular Dysplasia Among SCAD Patients in Cohorts With >100 Patients

First Author, Year (Ref. #)	N	% Screened for EVA	% FMD Among Those Screened	% Non-FMD EVA Among Those Screened	% Aneurysm
Tweet et al., 2014 (48)	189	59.8% (113/189)*	54% (61/113)	NR	NR
Eleid et al., 2014 (47)	246	45.5% (112/246)†	56.3% (63/112)	13.4% (15/112)‡	NR
Prasad et al., 2015 (73)	115	100%§	45.2% (52/115)	66% EVA, including FMD	22.5% cerebral aneurysm (9/40)
Saw et al., 2017 (60)	327	80.7% (264/327)‖	77.6% (205/264)	NR	14.1% (29/205) cerebral aneurysm among patients with FMD
Kok et al., 2018 (3)	585	57.2% (335/585)¶	58% (195/335)	22.6% (76/335)‡	10.7% (30/278) head/neck aneurysm, pseudoaneurysm; 8.1% (25/310) body aneurysm, pseudoaneurysm
Clare et al., 2019 (6)	208	43.2% (90/208)#	10% (9/90)	NR	NR
Sharma et al., 2019 (7)	113	30.1% (34/113)**	52.9% (18/34)	100% had EVA[3] (including FMD)	NR
Saw et al., 2019 (5)	750	54.8% (233/411)‖	56.7% (233/411)	NR	7.1% (30/424) cerebral aneurysm

*Distribution and modality of screening not described. †Screening by CTA, MRA, or invasive angiography. Distribution of screening not described. ‡EVA defined as FMD, aneurysm, dissection, arterial tortuosity. §95 of 115 patients underwent neck to pelvis CTA, 20 of 115 patients had limited imaging for FMD. ‖Catheter-based renal, iliac, cerebrovascular screening with pigtail catheter during coronary angiogram or CTA/MRA renal, iliac arteries; CTA/MRA head and neck. ¶Invasive angiography, CTA, MRA from brain to pelvis; 24.5% (82 of 335) of those screened had partial imaging. #Includes only those with head to pelvis imaging; modality not specified. **CTA head to pelvis.

CTA = computed tomography angiography; EVA = extracoronary arteriopathy; FMD = fibromuscular dysplasia; MRA = magnetic resonance angiography; NR = not reported.

traumatic stress disorder, and after AMI, women bear a greater burden of these symptoms (82–84). Risk markers for higher levels of psychological symptoms after SCAD include female sex, younger age, P-SCAD, and lower resiliency scores (83,84). Uncertainty about the causes of SCAD, inconsistent and inadequate management recommendations, lack of secondary prevention options, and loss of health-related locus-of-control all may contribute to the observed higher levels of distress, lower quality of life scores, and rehospitalization for cardiac events (85). Recognizing and addressing the high burden of psychological distress among SCAD patients and providing treatment, referral, and support for those who are distressed is critically important to their recovery.

RECURRENT SCAD

SCAD patients experience a high frequency of MACE driven primarily by recurrent SCAD. Rates of recurrent SCAD are variably reported (10% to 30%) depending on definition, study design, and time to follow-up. Recurrences many years after initial SCAD have also been reported (**Table 6**). Published reports have not consistently differentiated extension of an initial dissection from a new dissection, a distinction that is important for both prognostication and clinical care. The classification of recurrent SCAD should be reserved for an apparent new dissection in a location that does not suggest extension of a prior SCAD and is accompanied by ACS symptoms and biomarker elevation (86). Dissection flap and/or IMH extension most commonly occurs within the first 7 days after first presentation (5,14), but relying on arbitrary timeframes may contribute to misclassification. Contiguous dissection extensions may also be accompanied by symptoms, ECG, and biomarker changes consistent with new myocardial ischemia or infarction. The imperfect understanding of the natural history of dissection and SCAD healing calls for careful review of imaging studies and ultimately, clinical judgment to differentiate an extension from a new SCAD. Importantly, noninvasive imaging and assumptions are not substitutes for invasive angiography, where recurrence is suggested by new ECG or biomarker changes (2).

The factors associated with recurrence risk remain poorly characterized. Severe coronary tortuosity has been weakly correlated with recurrent SCAD, and highly tortuous segments may be more often affected (47). FMD, migraine headaches, beta-blockers, and the presence of hypertension have been variably associated with recurrence (6,60,61). No association has been observed between recurrent SCAD and treatment with antiplatelet agents or statins. In summary, aside from avoiding theoretical triggers such as extreme exertion or stress, hypertension control appears to be the most promising secondary prevention strategy for SCAD. Beta-blocker therapy, if tolerated, is also reasonable, but it should be recognized that the evidence for its use is limited to a single observational and retrospective cohort (60).

TABLE 6 Recurrent Spontaneous Coronary Artery Dissection

First Author, Year (Ref. #)	N	Atherosclerosis Included	Recurrence Definition	Excluded Extension?	Recurrence Rate
Tweet et al., 2014 (48)	189	No	New SCAD, clinical evidence of acute myocardial ischemia and biomarker increase	Yes	29/189 (15%) 27% 5-yr K-M estimate/Median follow-up 27 months IQR: 8.7 to 66.7 months Range 0.06 to 332 months
Lettieri et al., 2015 (4)	127	Yes (11.9% of series)	New SCAD, not further defined	Not discussed	6/127 (4.7%) Median follow-up 22 months Range 1 to 166 months
Nakashima et al., 2016 (11)	63	No	New SCAD not involving index vessel	Yes	8/63 (13%) Median follow-up 34 months Range 3 to 160 months
Rogowski et al., 2017 (99)	64	No	New SCAD not involving index vessel	Yes	3/64 (4.7%) Median follow-up 54 months IQR: 21.6 to 100.8 months
Saw et al., 2017 (60)	327	No	New SCAD with evidence of acute myocardial ischemia and biomarker increase	Yes	34/327 (10.4%) 12-19% 5-yr K-M estimate Median follow-up 37 months 17.9 to 65.9 months
Kok et al., 2018 (3)	585	No	New SCAD, clinical evidence of acute myocardial ischemia and biomarker increase	Yes	88/585 (15%) 17% 5-yr K-M estimate Median follow-up 31.2 months IQR: 11.8 to 64.2 months Range 0.95 to 346.9 months
Saw et al., 2019 (5)	750	No	New SCAD, clinical evidence of acute myocardial ischemia and biomarker increase	Yes	1/750 0.13% at 30 days
Clare et al., 2019 (6)	208	Unknown	New SCAD, not further defined	Not discussed	22/208 (10.6%) Follow-up 4.7 ± 3.1 yrs (5/22 recurrences occurred >60 months from index SCAD, 1 at 10.5 yrs)
Lobo et al., 2019 (100)	53	No	New SCAD presenting as STEMI after an initial SCAD (NSTEMI recurrence excluded)	Yes	0/53 0% at 1 yr
Krittanawong et al., 2020 (101)	1,836	Unknown, based on ICD codes only, no angiographic review	Patient with ICD-coded SCAD admitted within 1 yr with another primary coded diagnosis of SCAD	No	495/1,836 26.9% at 1 yr

ICD = International Classification of Diseases; IQR = interquartile range; K-M = Kaplan-Meier; NSTEMI = non–ST-segment elevation myocardial infarction; SCAD = spontaneous coronary artery dissection; STEMI = ST-segment elevation myocardial infarction.

REPRODUCTIVE AND GYNECOLOGIC CONCERNS

CONTRACEPTION. There is a paucity of evidence to guide recommendations regarding specific contraceptive methods, but risks associated with pregnancy exceed those of any form of contraception. In women who have completed their families, permanent sterilization of the patient (assuming medical candidacy) or partner often represents the best option. Highly effective forms of contraception are recommended, preferably avoiding estrogen-containing options as these may mimic a hormonal milieu similar to pregnancy. Long-acting progesterone-only methods (subdermal levonorgestrel implant) and levonorgestrel-releasing intrauterine devices (IUD) appear safe in women with cardiovascular disease and have very low (<1%) annual failure rate (87,88), although the safety profile of these methods has not been assessed after SCAD. The levonorgestrel IUD has the advantage of reducing menstrual blood loss, a particular issue for reproductive-age women on DAPT (89). The nonhormonal copper IUD remains an option, but often is associated with increased menstrual bleeding and slightly higher rates of unintended pregnancy. All barrier or periodic abstinence methods, even when used consistently, have relatively high failure rates compared with hormonal contraception and IUDs. If these are strongly preferred by couples, the addition of a spermicide to the barrier method may reduce rates of unintended pregnancy. The safety of emergency contraception in the post-SCAD population is unknown.

MENORRHAGIA ASSOCIATED WITH ANTIPLATELET THERAPY OR ANTICOAGULATION. Menorrhagia is a relatively frequent side-effect of DAPT. The levonorgestrel-releasing IUD simultaneously fulfills purposes of both contraception and reduction in uterine bleeding (90,91). If exogenous hormones are used, progesterone-only agents are a potentially

TABLE 7 Approach to the Pregnant Woman With Prior Spontaneous Coronary Artery Dissection

Pre-conceptual planning
1. Counseling with cardiology and maternal fetal medicine specialists to review risks of pregnancy in the context of the patient's medical history and current clinical status.
2. Review of symptoms, left ventricular function, and functional status. Consider stress testing.
3. Medication review: low-dose aspirin, clopidogrel, and beta-blocker medications do not appear to carry teratogenic risk, although beta-blockers have been associated with fetal growth restriction later in gestation; accordingly, all may be continued if clinically indicated angiotensin-converting enzyme (ACE) inhibitors and statin medications may be teratogenic, and are generally discontinued prior to conception or at time of identification of pregnancy (95).
At pregnancy diagnosis
1. If not recently assessed, cardiology consultation to assess symptoms, left ventricular function, and functional status.
2. Address the option and potential risks and benefits of pregnancy termination, especially if the pregnancy was unintended.
3. Medication review (as above).
4. Genetics referral for patients with potentially heritable syndromes.
Special considerations beyond routine prenatal care
1. Early ultrasound (7–8 weeks) to determine fetal viability, fetal number, and define gestational age.
2. Cardiac evaluation and maternal echocardiography: 8–12, 22–24, and 32–34 weeks gestation.
3. Anesthesiology consultation at 32–34 weeks.
4. Multidisciplinary team review at 34–36 weeks to determine location, timing, and method of delivery.
5. Discontinue clopidogrel at 36 weeks to permit option of intrapartum neuraxial anesthesia.
Delivery and early postpartum care
1. Delivery should occur at a level 3 or 4 perinatal center due to expedient subspecialty resource availability (102).
2. Scheduled delivery at 39–40 weeks gestation, optimally when providers familiar with individual patient care are collectively available. In the event of planned labor induction, specific intrapartum parameters include:
a. Early neuraxial anesthesia placement to reduce the catecholamine-mediated tachycardia associated with labor.
b. Avoidance of terbutaline (as a uterine relaxant) due to reflex tachycardia potentially increasing myometrial oxygen demand.
c. Consider delayed Valsalva maneuvers/passive descent ("delayed pushing") in the second stage of labor to optimize maternal venous return, with operative vaginal delivery reserved for standard obstetrical indications.
d. In the event of postpartum hemorrhage, avoidance of methylergonovine due to risk of coronary arterial spasm.
3. Per maternal preference, immediate postpartum bilateral tubal ligation may be considered.
4. If antepartum and intrapartum courses are uncomplicated, patients may be transferred to the routine postpartum ward with plan for expeditious evaluation of any cardiopulmonary symptoms.

better option than regimens containing estrogen, but may be accompanied by unpredictable menstrual bleeding patterns. When preserving fertility is not a goal, endometrial ablation, which can be performed safely in women who require DAPT or anticoagulation, is an attractive option.

PREGNANCY AFTER SCAD. Women are often advised to avoid pregnancy after SCAD, so there are few reports of maternal or fetal outcomes in these patients. In 1 series, 1 of 8 patients (13%) experienced recurrent SCAD 9 weeks postpartum requiring emergency CABG (92), and in another, 2 of 11 (18%) women had recurrent MI postpartum (93). The Mayo Clinic registry currently lists 31 pregnancies after SCAD in 22 women, with 19 (61%) resulting in live births. Preterm delivery occurred in 1 patient (5.3%), with a cesarean delivery rate of 37% (7 of 19). Two patients (11%) experienced recurrent SCAD at 9 weeks postpartum, and another experienced it years later. Fourteen patients (74%) elected to breastfeed; 2 discontinued due to concurrent angina and recurrent SCAD (94).

These data suggest that the majority of SCAD patients who subsequently conceive experience uncomplicated pregnancies. However, unlike pregnancy complications in women with heart failure or valvular heart disease, SCAD is unpredictable; cardiovascular testing and monitoring cannot prevent or assess risk for recurrent SCAD. A reasonable approach to those with a strong desire to become parents is to minimize risks for unplanned pregnancy and provide thorough pre-conception counseling, reviewing available data on pregnancy outcomes and focusing on individual maternal/fetal risks such as left ventricular function, residual cardiac symptoms, and teratogenic drug use (95). Due to the hormonal stimulation protocols required, there are potential and unknown risks of in vitro fertilization, whether or not a gestational carrier is used. "Natural cycle" (unstimulated) in vitro fertilization with a gestational carrier may be a safer option. A surrogate pregnancy with donor oocyte would preclude any maternal risks.

If, after comprehensive cardiovascular evaluation and medication review, patients elect to proceed with

conception or a woman becomes pregnant due to contraceptive failure, management should be coordinated by a multidisciplinary cardiology, maternal-fetal medicine, and anesthesiology team. Safety of pregnancy termination after SCAD is unknown, and similarly requires coordination by the multidisciplinary team. **Table 7** reflects an approach to antepartum management based on current practice and institutional experience.

CONCLUSIONS/FUTURE DIRECTIONS

The current document represents a summary of contemporary knowledge regarding SCAD. Increasing recognition of SCAD has improved our understanding of the disease process and highlighted shortfalls in objective evidence. Data remain retrospective, observational, and confounded by selection, survival, and reporting, among other biases. Progress will require prospective and collaborative evaluations across centers and geography, as exhibited among the authors of this review and engagement of patients. Specific high-impact areas for further study include:

1. Effects of sex, gender, race, and ethnicity on susceptibility to SCAD and the contributing roles of endogenous and exogenous hormones; concerted efforts to include more men and nonwhite individuals with SCAD in research studies will be required.
2. Determining optimal diagnostic technique(s) and criteria so as to consistently and accurately identify and differentiate SCAD from other causes of AMI, chest pain, and biomarker elevation.
3. Identification of appropriate indications and optimal techniques for revascularization.
4. Quantification of risks and benefits of the use of antiplatelet agents and other pharmacological therapies in both acute and convalescent timeframes.
5. Identification and individualization of risk factors for recurrent SCAD and other MACE, including temporal risk trends.
6. Development of molecular, cellular, and whole animal genetic model systems to gain mechanistic understanding of SCAD and its genetic variations.

Finally, there must be continued education to enhance awareness of the signs, symptoms, and importance of taking action to expeditiously evaluate symptoms of heart disease and accurately diagnose the etiology of ACS, especially among women.

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KEY WORDS fibromuscular dysplasia, genetics, myocardial infarction, pregnancy-associated, SCAD, women