ORIGINAL RESEARCH

Prevalence and Clinical Factors of Migraine in Patients With Spontaneous Coronary Artery Dissection

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***Background*—**Spontaneous coronary artery dissection (SCAD) is a cause of acute coronary syndrome predominantly in women without usual cardiovascular risk factors. Many have a history of migraine headaches, but this association is poorly understood. This study aimed to determine migraine prevalence among SCAD patients and assess differences in clinical factors based on migraine history.

***Methods and Results*—**A cohort study was conducted using the Mayo Clinic SCAD "Virtual" Multi-Center Registry composed of patients with SCAD as confirmed on coronary angiography. Participant-provided data and records were reviewed for migraine history, risk factors, SCAD details, therapies, and outcomes. Among 585 patients (96% women), 236 had migraine history; the lifetime and 1-year prevalence of migraine were 40% and 26%, respectively. Migraine was more common in SCAD women than comparable literature-reported female populations (42% versus 24%, $P<0.0001$; 42% versus 33%, $P<0.0001$). Among all SCAD patients, those with migraine history were more likely to be female (99.6% versus 94%; $P=0.0002$); have SCAD at a younger age (45.2±9.0 years versus 47.6±9.9 years; $P=0.0027$); have depression (27% versus 17%; $P=0.025$); have recurrent post-SCAD chest pain at 1 month (50% versus 39%; $P=0.035$); and, among those assessed, have aneurysms, pseudoaneurysms, or dissections (28% versus 18%; $P=0.018$). There was no difference in recurrent SCAD at 5 years for those with versus without migraine (15% versus 19%; $P=0.39$).

***Conclusions*—**Many SCAD patients have a history of migraine. SCAD patients with migraine are younger at the time of SCAD; have more aneurysms, pseudoaneurysms, and dissections among those imaged; and more often report a history of depression and post-SCAD chest pain.

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Spontaneous coronary artery dissection (SCAD) is an important cause of nonatherosclerotic myocardial infarction (MI) and sudden cardiac arrest, particularly among young and middle-aged women.[1] SCAD may account for as many as 4.0% of all acute coronary syndromes and 30% of acute coronary syndromes in women under 50 years of age.[2–4] SCAD occurs due to an intramural hematoma±intimal/medial tear in a coronary artery, which can impair blood flow to the myocardium with consequent MI and/or sudden cardiac arrest.[5] While the majority of SCAD occurs in a single coronary artery, it can also occur in several coronary arteries concurrently.[6] It may also recur weeks to years following an initial SCAD, the risk factors for which are not well identified.[2]

The recent evolution of social media networking[7] and diagnostic imaging techniques[8] has accelerated research efforts and improved SCAD recognition and awareness. Although many SCAD patients do not have classic atherosclerotic risk factors, recent studies have associated SCAD with fibromuscular dysplasia (FMD), pregnancy, severe emotional/mental stress, extreme physical exertion, coronary tortuosity, and connective tissue disorders.[5,6,9–12] However, the precise etiology of SCAD, along with effective preventative measures and long-term outcomes, remain unknown.

Migraine headaches have emerged as a condition found in SCAD patients.[11,13] SCAD cohort studies report migraine in

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Clinical Perspective

What Is New?

- Migraines are common among those who have had acute coronary syndrome due to spontaneous coronary artery dissection (SCAD), especially women.
- Within our SCAD cohort, those with migraines were younger at the time of SCAD; more often reported depression and post-SCAD chest pain at 1 month; and, among those imaged, had more arterial aneurysms, pseudoaneurysms, and dissections.

What Are the Clinical Implications?

- All SCAD patients should be assessed for comorbid conditions such as migraines, depression, and anxiety, and undergo at least one-time vascular imaging.
- A history of migraines can guide medication decisions, as migraines may be exacerbated by nitrates and be improved with β blockade.
- The association of SCAD, migraines, and vascular abnormalities such as fibromuscular dysplasia provides insight about possible SCAD pathophysiology, which likely represents a spectrum of arteriopathy.

37% to 46% of patients,[6,8,11,13] as compared with a lifetime prevalence of migraine of 24% in US women with stable angina from the WISE (Women's Ischemia Syndrome Evaluation) cohort.[14] In generally healthy populations, such as the GEM (Genetic Epidemiology of Migraine) cohort from the Netherlands, the lifetime prevalence of migraine is estimated at 25% to 33% in women and 8% to 13% for men.[15,16] Migraine headaches, based on patient self-report or headache criteria, are associated with an increased risk of cardiovascular events, such as ischemic stroke and MI.[17–20] Migraine is also increased in patients with other vascular abnormalities, such as intracranial aneurysms, cervical or vertebral artery dissections, and FMD.[21–24] In FMD cohorts, over 30% have migraine.[23] As migraine is frequently noted in these vascular conditions, it bears further investigation in SCAD. The primary objective of this study was to assess prevalence, presentation, clinical factors, and characteristics of patients with a history of both SCAD and migraine and compare them with patients who have had SCAD without a history of migraine.

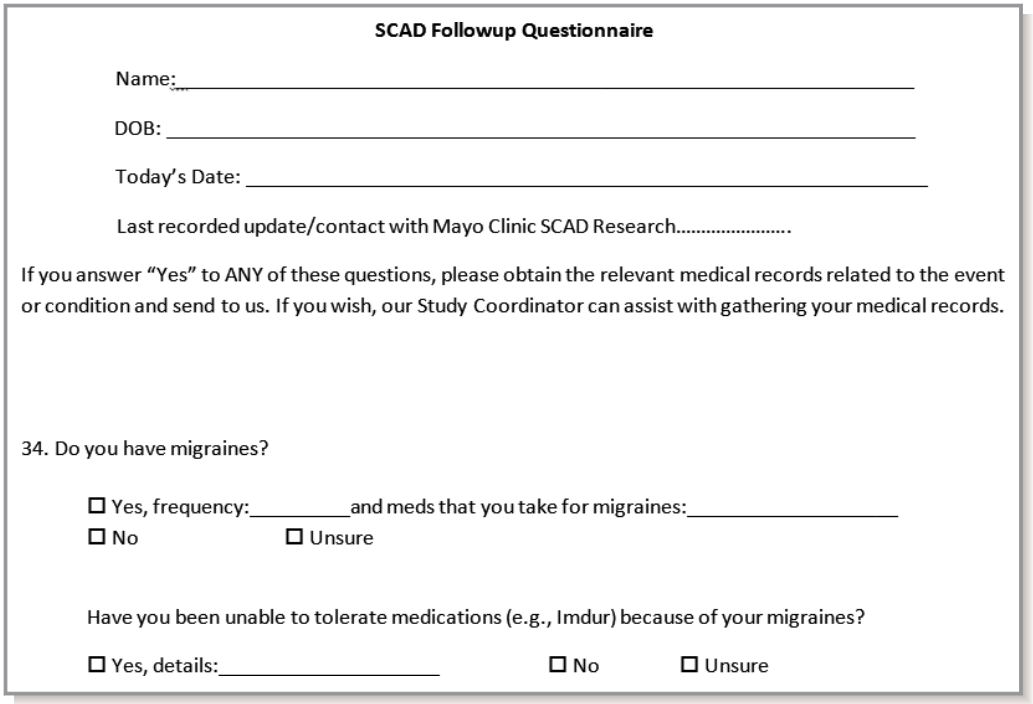
Methods

This study was approved by the Mayo Clinic Institutional Review Board. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The ongoing Mayo Clinic SCAD "Virtual" Multi-Center Registry, established in 2010, is an international registry of patients who experienced nonatherosclerotic SCAD as confirmed on review of coronary angiography images by 2 interventional cardiologists (RG, PB).[7,25] People with coronary artery atherosclerosis–related dissection or isolated iatrogenic dissection or who do not provide written informed consent are not included. Participants are recruited to the Mayo Clinic SCAD Registry by presenting with acute SCAD at a Mayo Clinic hospital during outpatient evaluation for SCAD in the dedicated Mayo Clinic SCAD Clinic, or by physician referral, social media networking, or patient word-of-mouth. Written informed consent, extensive questionnaires including a personal narrative of the SCAD event, medical records, and images are collected from participants and thoroughly reviewed. Patients are followed through clinic visits and/or intermittent questionnaires after registry enrollment. Of 718 patients enrolled from January 2010 to January 2017, 585 patients had complete questionnaires and records to be included in this study.

Patients with a history of migraine were identified (from self-report on questionnaires, documentation in medical records, and/or diagnosis from provider visit) and lifetime prevalence of migraine was calculated. Patients with ≤1 lifetime "migraine" event were not considered to have a migraine history.[26] Rare reports of "ocular" migraine were included (n=4). Demographic information, SCAD details, comorbidities, and treatments were compared between the 2 cohorts.

In addition to assessing lifetime migraine prevalence among all participants, we estimated the crude and age-adjusted cohort 1-year prevalence of active migraine, as is frequently reported in headache literature.[15,16,27] These data were extracted from follow-up questionnaires with specific questions about migraines (Figure 1) which were available for 231 participants in the study cohort. Those who did not have this additional data available (including patients not yet due for the follow-up questionnaire and those who did not yet return a follow-up questionnaire) were excluded from this portion of the analysis. Regarding frequency, most patients responded with a numerical response (eg, number of headaches per month), but nonspecific responses such as "rare" or "occasional" were assigned a rate of once per year (n=4). Responses were assumed to apply to the previous year to allow for age adjustment. Active migraine was defined as ≥1 migraine per year for the 1-year prevalence estimate.[28]

Another subset of participants had appropriate imaging available to assess for extracoronary vascular abnormalities (EVAs; n=335) defined as invasive angiography, computed tomography angiography, and/or magnetic resonance angiography of vascular beds from brain to pelvis,[11,29] 82 of whom had partial imaging. EVAs were defined as FMD, aneurysms, pseudoaneurysms, or dissections. Prevalence of EVAs, including FMD, was compared between those with and without



SCAD Followup Questionnaire

Name:_____

DOB: _____

Today's Date: _____

Last recorded update/contact with Mayo Clinic SCAD Research.....

If you answer "Yes" to ANY of these questions, please obtain the relevant medical records related to the event or condition and send to us. If you wish, our Study Coordinator can assist with gathering your medical records.

34. Do you have migraines?

☐ Yes, frequency:_____and meds that you take for migraines:_____
☐ No ☐ Unsure

Have you been unable to tolerate medications (e.g., Imdur) because of your migraines?

☐ Yes, details:_____ ☐ No ☐ Unsure

Figure 1. Excerpts from SCAD follow-up questionnaire referencing migraines.

migraine history. Those who did not have images available were excluded. Iatrogenic dissections were excluded.

Migraine-related medications at the time of enrollment in the SCAD Registry were also reviewed, including the following vitamins and supplements: magnesium, riboflavin (and B complexes), and coenzyme Q-10.[30] When available, migraine medication details immediately before and after the first SCAD hospitalization were collected retrospectively from contemporaneous medical records. Any available post-SCAD neurology referrals for migraine, at either the Mayo Clinic or other institutions, were reviewed.

Statistical Analysis

The data were analyzed using Excel version 14.0 (Microsoft Corporation, Redmond, WA), JMP version 13.0.0 (SAS Institute Inc, Cary, NC), and the R Foundation for Statistical Computing (Vienna, Austria). Ordinal and nominal variables were compared using Pearson's chi-squared test and continuous variables were compared using the Student's *t* test. Kaplan–Meier curves were generated using log-rank analysis to compare SCAD recurrence at 5 years, the primary outcome of interest. Linear regression for continuous variables, logistic regression for categorical variables, and Cox proportional hazard analyses were used for multivariable analyses with 95% CIs. Variables included in the multivariable analyses were age and sex, as those were significantly different among those with and without migraines, and hypertension, which is associated with increased SCAD recurrence in 1 observational study.[31] A post hoc, 2-sided power analysis was conducted using an α of 0.05, power of 0.8, assumed SCAD recurrence of 0.2 based on published data,[1] and hazard ratio of 2.[31] A 1-sample proportion test was used to compare the migraine prevalence values (both lifetime and 1-year) in our cohort with literature reported values.[14–16,27] The observed 1-year prevalence of migraine by age was compared with published 1-year female prevalence values by comparing observed and expected values. An age-adjusted standardized incidence ratio of migraines in SCAD patients was calculated by comparing observed migraines in SCAD patients to expected values of migraines in the general population using literature-reported values.[27] The standardized incidence ratio and 95% CIs were calculated using an exact Poisson test. Statistical significance was set at $P<0.05$.

Results

Patient Characteristics

The mean age of the total cohort (n=585) was 46.6±9.6; 96% of the patients were female and 94% were white. Although some patients had hypertension (n=215; 37%) and hyperlipidemia (n=207; 35%), the majority did not have traditional atherosclerotic risk factors (Table 1). Pregnancy and female hormone-related factors are detailed in Table 2.

Table 1. Baseline and Clinical Characteristics

	Total Cohort	No History of Migraine	History of Migraine		
	n=585	n=349 (60%)	n=236 (40%)	Unadjusted *P* Value	Adjusted *P* Value
Female	564 (96)	329 (94)	235 (99.6)	0.0007	0.0002
Age, y	46.6±9.6	47.6±9.9	45.2±9.0	0.0023	0.0027
White	549 (94)	329 (94)	220 (93)	0.60	0.87
Hypertension	215 (37)	127 (36)	88 (37)	0.83	0.57
Diabetes mellitus	22 (3.8)	14 (4.0)	8 (3.4)	0.70	0.55
Hyperlipidemia	207 (35)	130 (37)	77 (33)	0.25	0.45
Hx of smoking	160 (27)	102 (29)	58 (25)	0.22	0.35
Marfan or Ehlers-Danlos	15 (2.6)	7 (2.0)	8 (3.4)	0.30	0.30
History of dissection of other artery	74 (13)	39 (11)	35 (15)	0.19	0.30
History of stroke/TIA	18 (3.1)	9 (2.6)	9 (3.8)	0.40	0.48
Significant family hx of cardiovascular disorders	79 (14)	44 (13)	35 (15)	0.44	0.47
Family hx of aneurysm	121 (21)	68 (19)	53 (22)	0.38	0.44
Family hx head/neck aneurysm	48 (8.2)	29 (8.3)	19 (8.0)	0.91	0.84
Family hx of dissection	17 (2.9)	10 (2.9)	7 (3.0)	0.94	0.66
Family hx head/neck dissection	4 (0.68)	1 (0.29)	3 (1.3)	0.16	0.18
Presentation and management					
Cardiac arrest	64 (11)	39 (11)	25 (11)	0.83	0.67
PCI	256 (44)	153 (44)	103 (44)	0.96	0.72
CABG	58 (9.9)	34 (9.7)	24 (10)	0.87	0.76
Tortuous coronary vessels, n=504	426 (85)	241 (83)	185 (86)	0.36	0.15
Coronary territories					
Multivessel	115 (20)	73 (21)	42 (18)	0.35	0.14
Left main	42 (7.2)	25 (7.2)	17 (7.2)	0.99	0.71
Left anterior descending	353 (60)	209 (60)	144 (61)	0.78	0.81
Diagonal	20 (3.4)	13 (3.7)	7 (3.0)	0.62	0.49
Ramus	18 (3.1)	13 (3.7)	5 (2.1)	0.27	0.36
Left circumflex	91 (16)	61 (17)	30 (13)	0.12	0.12
Obtuse marginal	88 (15)	54 (15)	34 (14)	0.72	0.90
Right coronary	80 (14)	46 (13)	34 (14)	0.67	0.65
Right posterior descending	44 (7.5)	27 (7.7)	17 (7.2)	0.81	0.95
Right posterolateral	19 (3.2)	12 (3.4)	7 (3.0)	0.75	0.37
Outcomes					
Chest pain during month following SCAD	252 (43)	135 (39)	117 (50)	0.009	0.035
Recurrent SCAD, KM* 5-y estimate	17%	19%	15%	0.39	

Values presented as n (%) or mean±SD. CABG indicates coronary artery bypass graft; Hx, history; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection; TIA, transient ischemic attack.
*Kaplan–Meier method analysis.

Prevalence of Migraine Headaches

The lifetime prevalence of migraine in our SCAD cohort of 585 patients was 40% (female lifetime prevalence=42%). These patients were identified from self-report on SCAD registry questionnaires (n=178, 75%) and review of records (n=58, 25%).

Of those with completed follow-up questionnaires that included migraine frequency data, 60 of 231 had active

Table 2. Pregnancy and Hormonal Factors in the Female Cohort

	Female Cohort	No History of Migraine	History of Migraine	
	N=563*	N=329 (58%)	N=234 (42%)	*P* Value
Pregnancy-associated SCAD	74 (13)	40 (12)	34 (15)	0.41
Hx of gestational hypertension	83 (15)	45 (14)	38 (16)	0.40
Hx of preeclampsia/eclampsia	45 (8.0)	26 (7.9)	19 (8.1)	0.93
SCAD while menstruating	62 (11)	36 (11)	26 (11)	0.95
SCAD on exogenous hormones†	95 (17)	51 (16)	44 (19)	0.30
Postmenopausal SCAD, %	206 (37)	123 (37)	83 (35)	0.64

Values presented as n (%). Hx indicates history; SCAD, spontaneous coronary artery dissection.
*One woman was excluded from this analysis because she did not know reproductive or hormonal details about her SCAD.
†Includes hormonal birth control and postmenopausal hormonal therapy (including topical therapies).

migraine headaches (Figure 2), yielding a 1-year prevalence of migraine among SCAD patients of 26% (27% among women). The age-adjusted standardized incidence ratio for migraine in patients with SCAD compared with the literature-reported female population migraine prevalence was 1.37 (95% CI, 1.05–1.76; P=0.019),[27] indicating an estimated 37% higher age-adjusted 1-year migraine prevalence in SCAD patients (Table 3).

Comparison of Migraine Prevalence Among SCAD Patients to Other Non-SCAD Cohorts

We noted a higher prevalence of migraine among SCAD patients compared with the WISE cohort, some of whom had atherosclerotic disease and were of older age (40% in all/42% in females versus 24%; P<0.0001),[14] and the GEM cohort from the Netherlands (42% versus 33%; P<0.0001).[16] The 1-year migraine prevalence among SCAD patients in our cohort was more frequent in comparison to the 1-year migraine prevalence of 17.6% (P<0.001) among women from a US cohort,[27] but similar in frequency to the prevalence among females in the GEM cohort[16] (26% versus 25%, P=0.73). Demographic and other relevant data comparing these cohorts with our SCAD cohort are presented in Table 4. As compared with SCAD patients without migraine, SCAD patients with migraine were more likely to be female and less likely to be male in both unadjusted and adjusted analyses (0.4% versus 6%; P=0.0002). They were also younger at the time of dissection (45.2±9.0 years versus 47.6±9.9 years; P=0.0027), even when assessing the women only (P=0.0031) (Table 1, Figure 3).

Among the subset of patients screened for EVAs (n=335), 58% had FMD (n=195), 23% had additional non-FMD EVAs (aneurysms, pseudoaneurysms, and dissections; n=76), and 65% had any EVAs (n=219) (Table 5). Non-FMD EVAs were more common among SCAD patients with migraine compared

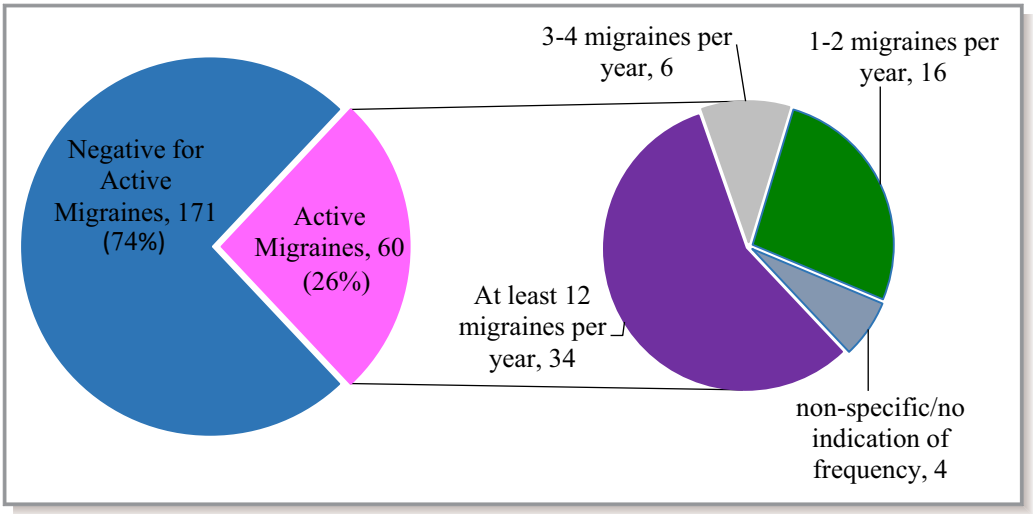


Figure 2. Figure diagramming the frequency of migraine headaches per year among patients with spontaneous coronary artery dissection (SCAD) and active migraine among 231 persons who responded to dedicated migraine survey questions.

Table 3. Age-Adjusted Standardized Incidence Ratio of Migraine Headaches in Patients With SCAD

Age, in Years, by Decade	Total With SCAD, n	Total SCAD With Migraine, n	Expected % With Migraine From Literature[27]	Expected Total in SCAD With Migraine, n	SIR	95% CI	*P* Value
All	231	60		44	1.37	(1.05–1.76)	0.019
30 to 39*	23	10	28.4	7			
40 to 49	67	20	25.8	17			
50 to 59	90	22	18.5	17			
60+	51	8	6.5	3			

Age-adjusted standardized incident ratio of migraine in SCAD patients compared with published literature values by age.[27] SCAD indicates spontaneous coronary artery dissection; SIR, standardized incidence ratio.
*One patient was 23, and she was included in the 30 to 39 age cohort. She had migraine headaches.

with those without migraine in the unadjusted analysis (28% versus 18%; *P*=0.025) (Figure 4); this difference remained after adjusting for age, sex, and history of hypertension (*P*=0.018). FMD or any EVA were not significantly different between the 2 groups on unadjusted analysis; however, any EVA was statistically significant when adjusting for age, sex, and history of hypertension (*P*=0.035).

History of depression (27% versus 17%; *P*=0.0053) and occurrence of recurrent chest pain during the month following SCAD (50% versus 39%; *P*=0.009) were higher among SCAD

Table 4. Comparison With Literature-Reported Cohorts Regarding Migraine Prevalence

	SCAD Cohort	WISE Cohort[14]	GEM Cohort[16]	AMMP Cohort[27]	*P* Value
Year	2018	2006	1999	2013	
Country	Primarily US	US	Netherlands	US	
Cohort size, n	585	905	6491	162 756	
White, %	94	82	96*	87	
Female, %	96	100	54	53	
Mean age, y±SD	46.6±9.6	58†	39.8±0.15	NR	46.6 vs 39.8, *P*≤0.0001
Age range, y	20–73	12–79	20–65	NR	
Major comorbidities	SCAD	94% with chest pain, 4.5% CAD	None	None	
Primary migraine assessment method	Self-report, general questionnaire	Self-report, general questionnaire	Self-report, headache specific questionnaires‡	Self-report, headache specific questionnaire	
Lifetime prevalence of migraine, %	All: 40 Female: 42	All/Female: 24		NE	All: 40% vs 24%, Female: 42% vs 24%, *P*≤0.0001
	All: 40 Female: 42		All: NR Female: 33	NE	Female: 42% vs 33% *P*≤0.0001
1-y prevalence of migraine, %	All: 26 Female: 27	NE	Female: 25		All: 26% vs 25%, *P*=0.73 Female: 27% vs 25%, *P*=0.51
				All: 12 Female: 17.3	All: 26% vs 12% *P*≤0.0001 All: 26% vs 17.3% *P*≤0.0005 Female: 27% vs 17.3% *P*≤0.0001

AAMP indicates American Migraine Prevalence and Prevention; CAD, coronary artery disease; F, female; GEM, Genetic Epidemiology of Migraine; NE, not evaluated; NR, not reported; SCAD, spontaneous coronary artery dissection; SD, standard deviation; WISE, Women's Ischemia Syndrome Evaluation.
*Ethnically Dutch population percent of the Netherlands in 1999 (available at https://opendata.cbs.nl/statline/#/CBS/en/dataset/03743eng/table?ts=15248 48061950; accessed on April 27, 2018) as the authors stated "the overwhelming majority of Netherlanders are white."[16]
†Standard deviation was not reported.
‡Participants were first evaluated with a mailed brief headache screen (stage 1), positive screens completed a more comprehensive migraine questionnaire (stage 2), then a random subset of screen positives from stage 2 was clinically interviewed (stage 3).[16]

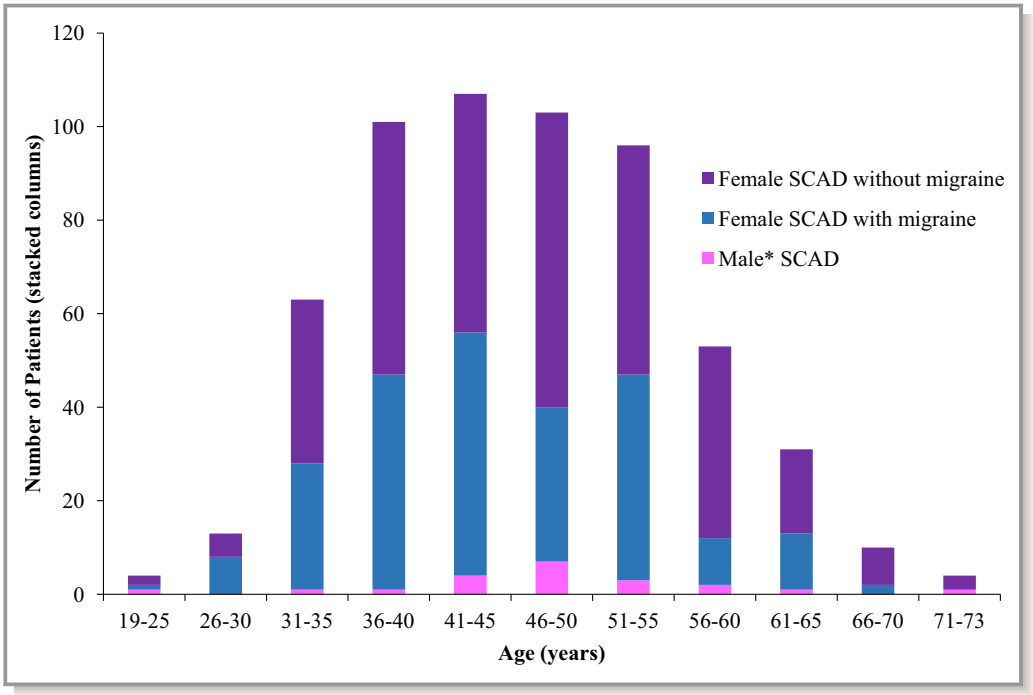


Figure 3. Distribution of patients based on age, sex, and migraine status. Spontaneous coronary artery dissection (SCAD) predominantly occurs from 30 to 60 years of age, with SCAD in those with migraine history tending to occur at a younger age compared with patients with SCAD but no migraine headache history. *One man had SCAD and history of migraine; he was age 50 at time of SCAD.

patients with migraine history compared with those without migraine history, respectively, and these results remained significant after adjusting for age, sex, and hypertension (P=0.025 and 0.035, respectively) (Tables 1 and 6). History of anxiety and concern for recurrent SCAD were significantly higher among those with migraines on unadjusted analysis

Table 5. Results in Cohort Screened for Extracoronary Vascular Abnormalities

	Total Screened Cohort	No History of Migraine	History of Migraine*	Unadjusted *P* Value	Adjusted *P* Value
	n=335	n=170 (51)	n=165 (49%)		
Any EVA[†]	219 (65)	104 (61)	115 (70)	0.10	0.035[‡]
Any FMD	195 (58)	96 (56)	99 (60)	0.51	0.32
Body FMD[§]	161 (52)	80 (52)	81 (52)	0.91	0.65
H/N FMD[‖]	77 (28)	32 (23)	45 (32)	0.10	0.08
Non-FMD EVA	76 (23)	30 (18)	46 (28)	0.025	0.018
H/N non-FMD EVA	40 (14)	17 (12)	23 (16)	0.33	0.34
H/N aneurysms/pseudoaneurysms	30 (11)	12 (8.7)	18 (13)	0.26	0.35
H/N dissections	18 (6.5)	10 (7.3)	8 (5.7)	0.60	0.77
Body non-FMD EVA	40[‖] (13)	17 (11)	23 (15)	0.31	0.24
Body aneurysms/pseudoaneurysms	25 (8.1)	12 (7.7)	13 (8.4)	0.83	0.82
Body dissections	20 (6.5)	8 (5.2)	12 (7.7)	0.36	0.21

Values presented as n (%). EVA indicates extracoronary vascular abnormalities; FMD, fibromuscular dysplasia; H/N, head and/or neck.
*Proportionally more of those with migraine history underwent vascular screening compared with those without migraine history (70% [55% full/15% partial] vs 48% [35% full/13% partial], respectively; P=0.02 for both any imaging and full imaging).
[†]Extracoronary vascular abnormalities including aneurysm, pseudoaneurysm, fibromuscular dysplasia, or dissection on imaging.
[‡]The other covariates may be driving the relationship between any EVA and migraine on the multivariable analysis.
[§]n=310 screened.
[‖]n=278 screened; four patients had both H/N non-FMD EVA and body non-FMD EVA, and were included in each group.

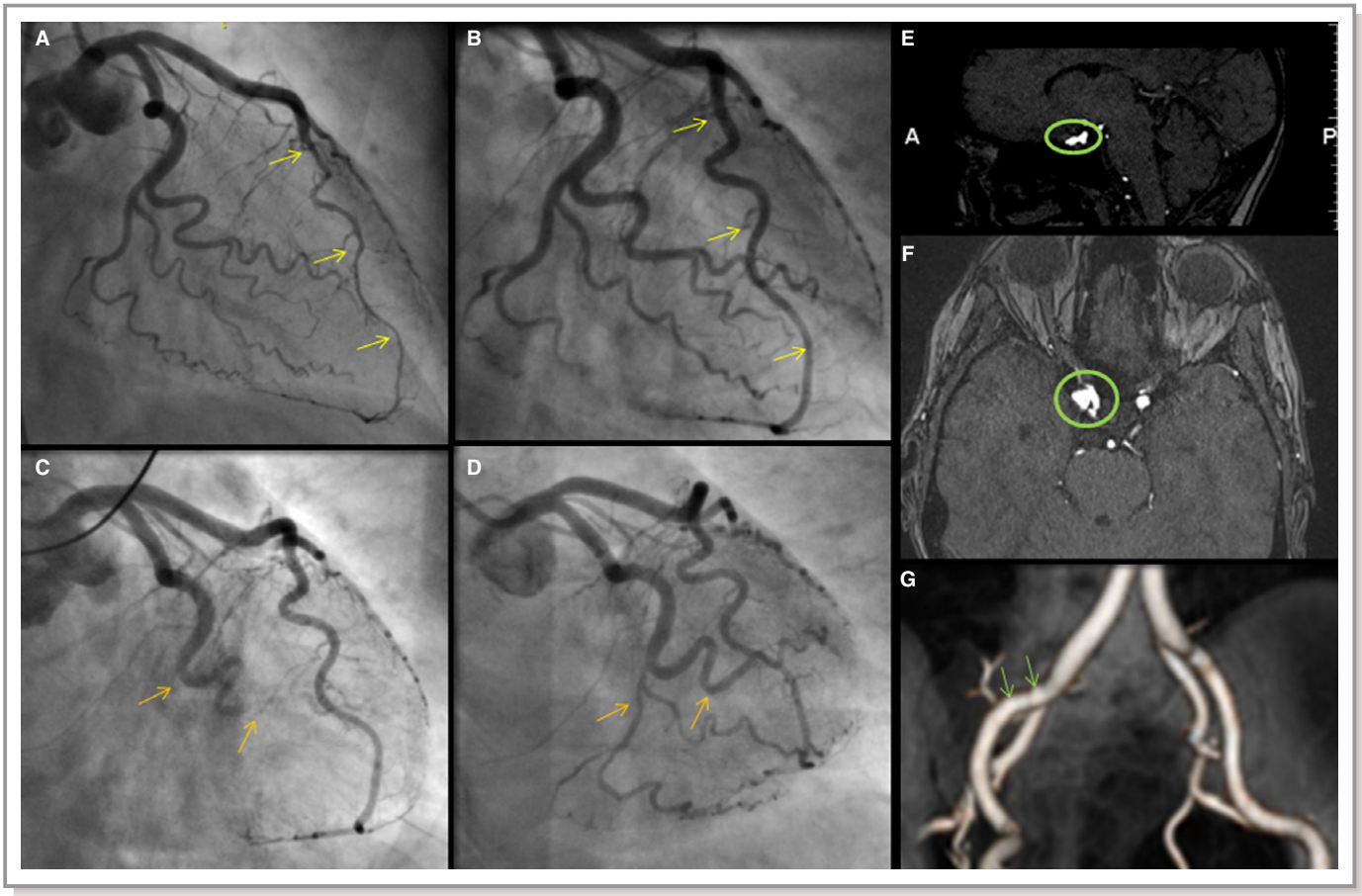


Figure 4. Imaging of vascular abnormalities and recurrent SCAD in a patient with migraine. This 55-year-old female's initial spontaneous coronary artery dissection (SCAD) caused an intramural hematoma of the left anterior descending coronary artery (**A**, arrows); follow-up coronary angiography demonstrated interval healing (**B**, arrows). Several years later, she presented with SCAD of the left circumflex with occlusion of the first obtuse marginal, distal circumflex and its branches (**C**, arrows). Despite an unsuccessful percutaneous intervention attempt, follow-up coronary angiography showed interval healing (**D**, arrows). She also was found to have a 7-mm right periophthalmic cavernous carotid aneurysm (**E** and **F**), 3-mm left cavernous internal carotid artery aneurysm, 2- to 3-mm right cavernous internal carotid aneurysm, and mild fibromuscular dysplasia of the right external iliac artery (**G**).

(32% versus 24%, *P*=0.040; and 46% versus 37%, *P*=0.031, respectively), but these associations did not remain significant when adjusting for age, sex, and hypertension. By Kaplan–Meier methods, the combined 5-year SCAD recurrence incidence was 17.2%. There was no statistically significant difference in 5-year recurrent SCAD incidence (15% versus 19%; *P*=0.39) between those with migraine and those without migraine (Figure 5) even when adjusting for sex, age, and

Table 6. Mood and Psychological Characteristics.

	Total Cohort	No History of Migraine	History of Migraine		
	n=585	n=349 (60%)	n=236 (40%)	Unadjusted *P* Value	Adjusted *P* Value
History of depression	125 (21)	61 (17)	64 (27)	0.0053	0.025
History of anxiety	159 (27)	84 (24)	75 (32)	0.040	0.14
Effective at stress management	409 (70)	250 (72)	159 (67)	0.27	0.33
Stress enough to affect health	239 (41)	134 (38)	105 (44)	0.14	0.18
Stress enough to affect QOL	204 (35)	112 (32)	92 (39)	0.086	0.15
Concern for recurrent SCAD	239 (41)	130 (37)	109 (46)	0.031	0.17
Concern for sudden cardiac death	165 (28)	94 (27)	71 (30)	0.41	0.72

Values presented as n (%). QOL indicates quality of life; SCAD, spontaneous coronary artery dissection.

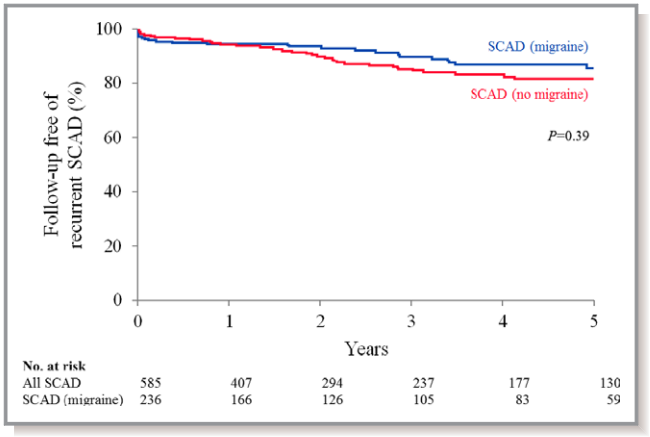


Figure 5. 5-year incidence of SCAD recurrence among patients with and without migraine history. No statistically significant difference was found in the Kaplan–Meier survival curve for SCAD patients with migraine (blue line) and that of SCAD patients without migraine (red line) (P=0.39).

history of hypertension (risk ratio, 0.74; 95% CI, 0.44–1.23). Post hoc power analysis assuming a recurrence of 20% and hazard ratio of 2 determined 69 required events for 80% power, which was less than the 88 recurrent SCAD events observed in the cohort.

Migraine Management

A total of 161 patients with migraine history (68% of the cohort with SCAD and migraine) had comprehensive information available on migraine medications immediately before and after SCAD. Of these, 33 (20%) were taking triptans before SCAD. After SCAD MI hospitalization, triptans were discontinued in 39% of patients (n=13).

The most common migraine-related medications taken by patients with SCAD and migraine history at time of enrollment in the SCAD Registry were β-blockers (n=140; 59%); <1% were on vasoconstrictors. At the time of enrollment in the SCAD registry, a majority were on aspirin therapy (n=210; 89%), most frequently dosed at 81 mg/day. Incidentally, among migraineurs, headache-related concern about nitrate medications was sometimes documented or reported by patients (n=29) and some migraineurs (n=16) commented on subjective improvement in headaches following SCAD.

Neurology referral information was available on 44 patients with SCAD and migraine; of these, 23 patients were seen at 28 visits for headache management. The other 21 patients were referred for other complaints, such as transient ischemic attack, head and/or neck aneurysms or dissections, or dizziness. Recommendations to avoid vasoconstrictors, such as triptans, were made in 10 of 28 visits (36%). Gabapentin was most often recommended for migraine prophylaxis (n=9; 32%). Acute management medications most often suggested were nonsteroidal anti-inflammatory drugs (n=7; 25%) and antiemetics (n=7; 25%).

Discussion

The primary findings in our study are as follows: (1) both the lifetime prevalence and 1-year prevalence of migraine were higher in this cohort of patients with SCAD as compared with literature-reported prevalence values[14,16,27]; (2) among those assessed, patients with SCAD and migraine more commonly have non-FMD EVA compared with patients without migraine history; (3) migraine history does not appear to incur greater risk of recurrent SCAD at 5 years; (4) when compared with those without migraine history, SCAD patients with migraine history are more often female, younger at the time of SCAD, and more commonly have recurrent chest pain at 1 month following SCAD and history of depression.

We report the first, to our knowledge, large study to investigate migraine in those with SCAD. Smaller SCAD cohorts have previously noted migraine headaches in 37% to 46% of patients.[6,11,13] However, these cohorts do not distinguish lifetime or 1-year prevalence of migraine or compare SCAD patients with migraine to SCAD patients without migraine. The Australian SCAD cohort does not specify 1-year versus lifetime prevalence and reports a migraine prevalence of 43% among 40 patients with SCAD,[13] which is similar to the lifetime migraine prevalence in this large and comprehensive SCAD cohort of 585 patients.

As migraine represents an important comorbid condition among SCAD patients, consideration of the link between migraine and other vascular conditions may yield insights into SCAD pathophysiology. Migraine headaches are associated with vascular phenomena such as aneurysms, retinal vasculopathy, reversible cerebral vasoconstriction, cervical and vertebral artery dissections, myocardial infarction, and stroke.[17–22,24,28,32–34] Systemic vascular changes in migraineurs include increased aortic stiffness indicating large-artery dysfunction[35] and increased activity of extracellular proteins such as elastase and matrix metalloproteinases.[36,37] Some studies suggest that endothelial dysfunction may contribute to conditions such as stroke and cervical artery dissection in migraineurs.[36,38–40] Supporting this association, a recent migraine genome study identified multiple loci related to vascular and endothelial genes.[41] Cervical artery dissection genomic studies have also identified loci that overlap with ones associated with migraine, such as PHACTR1 (also associated with FMD) and LRP1, both of which code for vascular function–related proteins.[13,41,42]

In the context of SCAD and migraine, these considerations are particularly intriguing given the finding that non-FMD EVAs (and all EVAs on adjusted analyses) were more common in

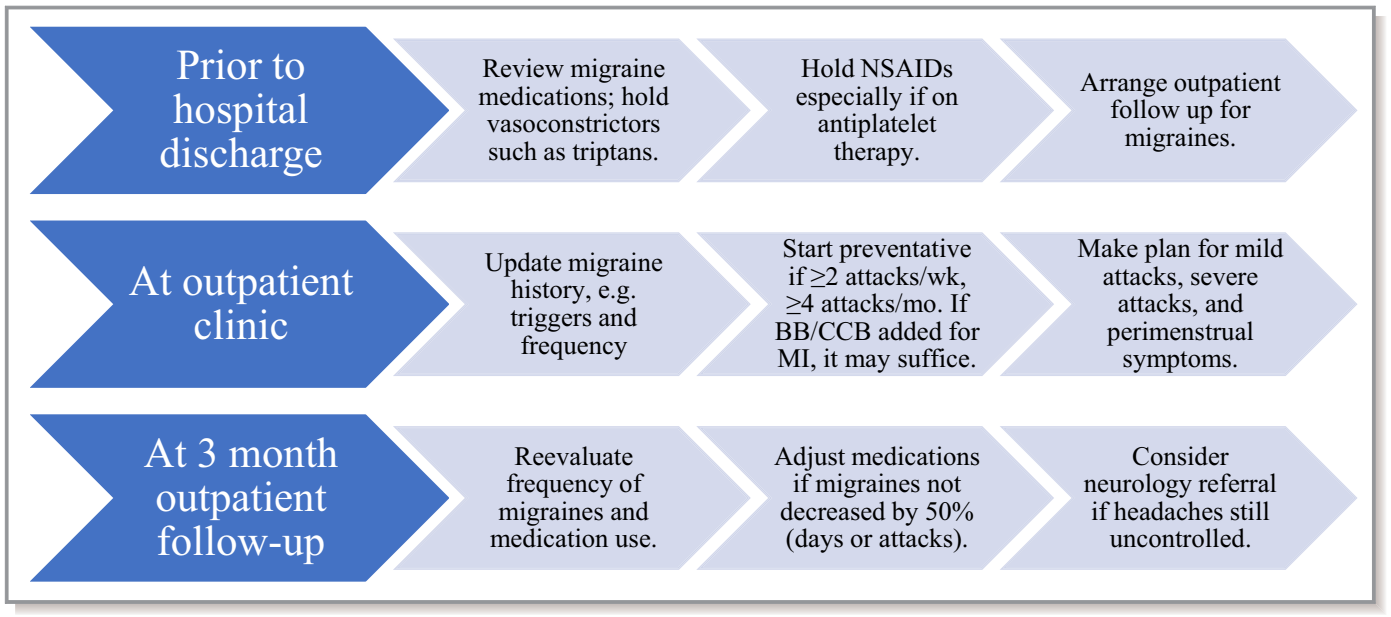


Figure 6. Recommendations for management of migraine post-spontaneous coronary artery dissection (SCAD). This general approach, based on this study's observations, the Mayo Clinic SCAD Clinic experiences, and recommendations from neurology literature, is not meant to be comprehensive and individualization of treatment is required.[60–63] BB indicates β-blocker; CCB, calcium-channel blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

SCAD patients with migraine. Upon stratification based on location or type of EVA, statistically significant differences were lost, likely due to insufficient sample sizes. Nevertheless, this strengthens the supposition that migraine, SCAD, and arteriopathies including EVAs and FMD, are indicative of an underlying systemic propensity to vascular injury and/or dysfunction, and in some may include genetic predispositions.[13,23,36,38,43]

Whatever the baseline characteristics of the vasculature, it stands to reason that other factors must also be involved. One potential factor may be hormonal changes in women.[18] Migraine headaches are associated with the menstrual cycle in over 50% of women.[44,45] A peak in frequency of migraine without aura has been correlated with the fall in estrogen (and progesterone) that triggers menstruation.[44,46,47] Hormonal decline has also been suggested as a possible inciting trigger for menstrual-related post-SCAD chest pain[48] and pregnancy-associated SCAD, which occurs most frequently during the first weeks postpartum.[5,12]

At present, although exogenous hormones can be safely used to control some types of migraine,[49,50] they are often discouraged post-SCAD due to uncertainty about risk. As estrogen is known to have multiple vascular effects,[51] further research into hormonal influences in migraine and SCAD is critical to identify shared mechanisms of disease and clarify the potential harms and benefits of hormonal substances in both conditions.[49]

Interestingly, we found an increased incidence of recurrent chest pain among those with SCAD and migraine compared with other SCAD patients (although overall both groups had frequent chest pain following SCAD). This may be related to increased global sensitivity to pain, which has been noted among migraineurs.[52,53] Endothelial dysfunction, coronary vasospasm, and microvascular disease can cause nonatherosclerotic chest pain,[54] but the role of these processes in SCAD is poorly understood. Even though post-SCAD chest pain often responds to antianginal medication, such as nitrates,[5] the use of nitrates may exacerbate headaches. Such limitation in therapeutic options could contribute to more prevalent recurrent chest pain among patients with SCAD and migraine.

Depression, known to be common among those who have experienced SCAD,[55] was more frequent among SCAD patients with migraine. Migraine is associated with an increased prevalence of mood disorders,[56] and the coexistence of depression with migraine is associated with greater migraine-related disability.[57] Both anxiety and depression are known to increase cardiovascular disease risk.[58] Our findings stress the importance of identification and appropriate management of mood disorders in patients with SCAD, especially migraineurs, in an effort to reduce the risk of future disability and harm.

In patients with migraine, triptans were infrequently discontinued at time of SCAD. Although only case reports have linked SCAD to vasoconstricting migraine abortives,[59] the use of such medications in those with cardiovascular disease is generally contraindicated.[60–63] Providers who care for patients with SCAD and migraine should review migraine

medications and consider discontinuing triptans. Subsequent referral to neurology may be necessary, as many migraineurs rely on these medications for acute headache relief. Of note, migraine headaches have been noted to improve after SCAD, possibly related to medications frequently added following SCAD such as β-blockers, which also have migraine prophylactic effects.[61] A similar phenomenon has been noted following cervical artery dissection.[64]

There are no established guidelines for managing migraine in patients with a history of cardiovascular disease. Generally speaking, risk factors such as smoking should be addressed, β-blockers or angiotensin receptor blockers should be used as indicated following MI,[34,61] and vasoconstricting abortives should be avoided.[60–63] Figure 6 includes our brief migraine management recommendations.

Limitations

Limitations of this study include selection and recall bias due to use of a registry and the cohort study design. Regardless, this is a substantial cohort of SCAD patients encompassing a large geographic representation, which includes information that would not otherwise be known in this population.

Another potential limitation is that migraines in this study were defined both subjectively as self-report on surveys and objectively as recorded in the medical record; this variation may lead to an inaccurate overall prevalence of migraines. However, self-report of migraines commonly occurs in the medical literature,[14,23,28,65] and less than half of patients meeting criteria for migraine obtain a medical diagnosis.[66,67] Patient self-report of migraine and International Classification of Headache Disorders II headache criteria have been shown to have fairly good agreement of 72%.[65] Therefore, we used both subjective and objective approaches to migraine diagnosis in an attempt to capture the most complete compilation of migraineurs.

Aura status is associated with worse outcomes among those with migraines[68,69] but was not consistently collected in this cohort. Even though this is a common limitation among published migraine studies,[14,17,70] we intend to incorporate aura-related data and additional composite outcomes of interest into future studies.

Only a subset of patients was imaged for systemic vascular abnormalities, and some patients had incomplete imaging limiting the data available for comparison among the 2 groups. A greater proportion of those with migraine underwent vascular imaging, which was likely clinically driven, although comprehensive vascular imaging is recommended for all patients following SCAD.[1,5] Patients diagnosed with FMD should be cared for clinically according to current recommendations.[70]

Conclusions

Migraine headaches are frequent in SCAD, and this observation raises the question of a possible underlying vascular propensity to injury, potentially modified by hormonal or genetic factors, as other vascular studies have hypothesized. Migraineurs with SCAD are more likely to report a history of depression and recurrent chest pain at 1 month but do not appear to be at higher risk for recurrent SCAD at 5 years. As SCAD research continues, further investigation into this newly characterized association between migraine and SCAD may significantly impact our understanding of mechanisms of disease and clinical management decisions, particularly related to systemic vascular abnormalities, recurrent angina, mood disorders, and migraine medications.

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Disclosures

None.

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