JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 80, NO. 17, 2022

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Spontaneous Coronary Artery Dissection

Lower Than Expected Recurrence Rate in a Large Prospective Canadian Cohort*

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Spontaneous coronary artery dissection (SCAD) is an important and previously underrecognized cause of acute coronary syndrome with a high female sex predominance.[1,2] Observational, mostly retrospective series have provided key insights into this disease, but interpretation has been challenged by the inevitable risk of patient selection leading to bias in registry analyses.

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In this issue of the *Journal of the American College of Cardiology*, Saw et al[3] report the 3-year outcomes of the Canadian Spontaneous Coronary Artery Dissection (SCAD) Cohort Study. This is a follow-up of the initial 2019 report describing the baseline characteristics of the cohort as well as in-hospital and 30-day outcomes.[4] The Canadian SCAD cohort represents an impressive effort, with inclusion and prospective follow-up of 750 patients with SCAD at the milder end of the previously reported spectrum of disease. This study established that SCAD should no longer be considered a rare disease, and the diagnosis should even be considered in older subjects and subjects with the typical risk factors for ischemic heart disease.[5]

The key new finding in this 3-year outcomes report of the Canadian SCAD registry is a much lower rate of de novo SCAD recurrence at just 2.4% in 1.9% of patients after 3 years.[3] This is at least 4-fold lower than initially reported, both by Saw et al[6] (10.4% during a 3.1-year median follow-up) and other groups[7-10] but consistent with other studies, particularly more recent and/or prospective series[11-16] (**Table 1**). Notably, in the previous study by Saw et al,[6] the proportion of patients on beta-blockers and aspirin both at discharge and follow-up was high, similar to that in the present study.

Most major adverse cardiovascular events (MACE) reported after SCAD in the current study[3] are attributable to the index event, with less than one-half of the 14% reporting 3-year MACE occurring >14 days after presentation. Death after recruitment was very rare, affecting 0.8% of cases (presumably some of which were noncardiac causes of death). Finally, there was a low rate of stroke/transient ischemic attack (2.3%). This was not broken down by severity or etiology but is consistent with previous evidence that extracoronary arterial abnormalities associated with SCAD seldom lead to clinically relevant complications.[17] Overall, these data will provide some reassurance to patients.

In a prospective cohort study, few significant recurrences are likely to have remained undetected. It is therefore more likely that the low prevalence of SCAD recurrence in the present prospective cohort[3] reflected the inclusion of less severe cases compared with registry-based observational series, due to the increasing ability of interventional cardiologists to recognize and include milder forms of this disease.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of the *Journal of the American College of Cardiology* or the American College of Cardiology.

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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 Author Center.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2022.09.004

TABLE 1 Comparison of the Prevalence of MACE and Recurrent SCAD in the Canadian SCAD Cohort Study and Other Previous Observational Studies

First Author, Ref. #, Year	N	Median Follow-Up (mo)	Design	MACE	Death	Recurrent MI	Recurrent SCAD	Stroke/TIA
Saw et al,[3] 2022 (current study)	750	36	Prospective	8.4	0.7	5.7	2.1	1.5
Tweet et al,[7] 2014	189	28	Retrospective	NR	0.5	NR	14.2	NR
Lettieri et al,[11] 2015	134	22	Retrospective/prospective	9.7	3.1	1.6	3.7	0.0
Nakashima et al,[8] 2016	63	34	Retrospective (database search)	38.0	1.6	25.4	19.0	NR
Rogowski et al,[12] 2017	64	54	Prospective	7.8	0.0	4.7	4.7	NR
Saw et al,[6] 2017	327	37	Prospective	19.9	1.2	16.8	10.4	1.2
Clare et al,[9] 2019	208	56	Retrospective (database search)	NR	3.3	NR	10.6	NR
Tweet et al,[10] 2020	636	38	Registry	NR	0.3	NR	14.8[a]	NR
Mori et al,[15] 2021	302	22	Retrospective	15.9	0.3	11.9	3.3	0.7
Combaret et al,[13,14] 2021/2022	373	12	Prospective	12.3	0.0	NR	3.3	0.3
Garcia et al,[16] 2022	389	29	Prospective	13.0	2.5	7.6	2.0	1.0

Values are % unless otherwise indicated. All events occurring from discharge to the last follow-up visit. [a]Recurrence occurring at least 1 month after the initial spontaneous coronary artery dissection (SCAD) event.

MACE = major adverse cardiovascular events; MI = myocardial infarction; NR = not reported; TIA = transient ischemic attack.

This is consistent with the high proportion of single-vessel (86.9%), single-segment (74.8%) disease, the low rate of left main coronary involvement (1.5%) at enrollment, and the high rate of conservative treatment (84.3%) in this cohort.[4,5]

In their original paper,[4] Saw et al sought to use multivariate analyses to predict MACE in-hospital and at 30 days. In the present paper,[3] an analysis at 3 years was undertaken. Interpretation is challenging as the MACE events included will be a heterogeneous combination, comprising a significant proportion of those events already reported in the previous analyses (and largely related to the index SCAD), as well as longer-term events, including recurrence. In all analyses (in-hospital, 30 days, and 3 years), pregnancy-associated SCAD is predictive of events, a finding consistent with other reports showing that pregnancy-associated SCAD is associated with a more severe presenting phenotype.[18,19] This likely leads to a higher risk of MACE events, especially those occurring early.

In the present report,[3] 2 further "independent predictors" of 3-year MACE, namely genetic disorders and presence of extracoronary fibromuscular dysplasia (FMD), are reported. Despite an impressive OR of 5.0 but with a large CI, the association with genetic disorders seems questionable. The genetic disorders included conditions not known to be related to SCAD (myotonic dystrophy, Charcot-Marie-Tooth, and genetic dilated cardiomyopathy). It is not clear if the adverse events seen were driven by genes known to cause SCAD, or whether the significance of the association with 3-year MACE would have been maintained after exclusion of these likely unrelated entities. Likewise, inclusion within "connective tissue disorders" of both inherited conditions such as Marfan syndrome and inflammatory autoimmune conditions such as rheumatoid arthritis makes interpretation of findings related to this combined disease group difficult. It should be noted that recent work has suggested there is no increased prevalence of autoimmune diseases in patients with SCAD.[20]

Finally, the authors state that extracoronary FMD is an independent predictor of 3-year MACE.[3] However, there are a number of factors suggesting that the data in this regard are not robust enough to make this claim. The *P* value was borderline, and OR was very low. Most importantly, only 58% of patients underwent complete screening for extracoronary FMD, and 23% of patients were not screened at all. It is not known why some patients were screened for FMD and others were not; therefore, potential exists for selection bias. In the absence of a core laboratory, assessment of FMD was performed at each center, without blinding, using different imaging modalities and potentially heterogeneous diagnostic criteria.[3,4] The reported incidence of FMD is substantially higher (56.4% in fully explored patients) than in the only single-blind analysis to include both patients with SCAD and healthy control subjects performed thus far (31.8%),[17] which may suggest overdiagnosis.

We strongly recommend that every patient with SCAD be screened from the head to pelvis 1 time with either computed tomography angiography (our preference) or magnetic resonance angiography (which can miss mild FMD). The importance of screening is not only to identify FMD but also other extracardiac manifestations such as aneurysms and dissections.

We have shown that 41% of patients with FMD have an aneurysm or dissection in at least 1 arterial bed.[21] These findings also occur, albeit less commonly, in patients presenting primarily with SCAD.[17] In addition, patients with SCAD may not exhibit the typical "string of beads" present in FMD[22] but may have all of the other manifestations mentioned earlier.

In this study,[3] neither antiplatelets nor beta-blockers significantly affected 3-year risk of MACE. This is contrary to previously reported findings from a retrospective registry analysis by the same group.[6] While the latest findings generate more uncertainty about the utility of these medications after SCAD, prospective randomized controlled trials are underway to address this question.[23] However, investigators should be aware of the potential impact of the low event rates reported in this study[3] on their sample size calculations.

Overall, and despite limitations, the present 3-year follow-up of the Canadian SCAD cohort[3] suggests a better prognosis and decreased SCAD recurrence rate in less selected, more representative SCAD patients. It deserves a close analysis by all those interested in diagnosis and care of patients with SCAD and provides further motivation for clinical trials in this disease.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Adlam has received research funding from Abbott Vascular to support a clinical research fellow; has received funding from AstraZeneca for unrelated research; and has undertaken consultancy for General Electric to support general research funds. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS myocardial infarction, spontaneous coronary artery dissection, women