

New European insights on spontaneous coronary artery dissection (SCAD): are we any closer in our scientific exploration voyage?

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Spontaneous coronary artery dissection (SCAD) is an incompletely understood cause of myocardial infarction (MI) and, although previously perceived as rare, it is increasingly recognised as an important cause of MI in young to middle-aged women. Scientific knowledge and publications on this disease have expanded tremendously in the past decade. Research derived from multicentre prospective and retrospective registries has helped to elucidate the clinical presentation, associated conditions, natural history, outcomes and prognosis of this challenging disease. We now understand the major predisposing causes for SCAD, including fibromuscular dysplasia (FMD), and precipitating factors that can provoke SCAD in the setting of weakened arterial walls. There have also been substantial investigations in the past five years on the genetic basis of SCAD, including novel genetic markers that link to FMD. There is genetic heterogeneity in the aetiology of SCAD and FMD, with a range of genetic effects including associated genes with monogenic effect (rare), and genome-wide significant common variant associations¹. Another important advance is the improved recognition of SCAD on angiography, facilitated by intracoronary imaging to help understand unique angiographic

appearances that are different from atherosclerosis. The establishment of a SCAD angiographic classification and algorithm for invasive workup has enhanced clinical diagnosis², which has contributed substantively to the increased prevalence of SCAD in the past half-decade. The accrual of more cases allows investigators to explore and understand the natural history and prognosis of this disease further, and also ultimately test treatment strategies in randomised controlled trials, something which is currently lacking. There remain many unknowns with this disease. Ongoing research in registries and clinical trials is much required to expand our understanding of this challenging disease. This current issue of EuroIntervention includes two publications from European registries that further address the knowledge gaps concerning this disease, and allow comparisons with different cohorts in North America^{3,4}.

Combaret et al summarised their findings from the observational DISCO registry (NCT02799186), which enrolled SCAD patients retrospectively and prospectively from 51 French cardiology centres³.

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They included 373 cases which were core laboratory adjudicated with the original Saw angiographic classification. Patient characteristics were similar to contemporary SCAD series, including a mean age of 51.5 years, ~90% women and ~60% with precipitating stressors. Type 2 angiographic SCAD was most common (70.4%), followed by type 1 (14.6%) and type 3 (8.6%); 19.0% had Thrombolysis In Myocardial Infarction (TIMI) 0 flow indicating vessel occlusion. The majority of patients (84.2%) were treated conservatively; only 15.5% underwent percutaneous coronary intervention (PCI). Interestingly, repeat coronary angiography was performed quite frequently in this cohort: 54 patients had early repeat angiography at a median 5 days, and 200 patients had delayed angiography at a median 56 days. Improvement in angiographic SCAD was observed in 66.7% at early angiography, and in 93% at delayed angiography, confirming findings from prior reports about spontaneous angiographic healing in the majority of cases⁵. Of note, iatrogenic catheter-induced dissection occurred in 1.9% of cases, which was similar to the high 3.4% rate observed in our series⁶. The one-year follow-up composite rate of death, stroke, SCAD recurrence (3.3%), infarction, and revascularisation was 12.3%. Radiologic screening for FMD in at least one non-coronary arterial bed was performed in 91.1% of patients (mostly by CT angiography) with 74.3% having a complete screen, and FMD was confirmed in 45% of patients, also in line with prior studies⁷. Men had FMD in 65.7% of cases, a finding which is striking when considered against the very low rates of FMD in men in the general population⁸. Genetic analysis was performed in 313 SCAD patients and compared against healthy controls from the French Paris Prospective Study III database. They found the PHACTR1 A-allele to be associated with increased risk of SCAD (OR 1.66, 95% CI: 1.38-1.99), confirming findings from prior studies^{1,9}. This increased risk estimate remained significant regardless of the presence or absence of diagnosed FMD, reiterating that the genetic association between SCAD and PHACTR1 locus is not fully explained by the association with FMD. In summary, this is a well-conducted SCAD registry from France with many important clinical and genetic findings that confirm prior studies, especially those from North America.

Mori et al reported their retrospective series of 302 SCAD patients from 23 Italian and Spanish centres from the DISCO IT/SPA registry (NCT04415762)⁴.

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This paper focused primarily on angiographic subtypes and correlation to outcomes, as prior studies have raised the suggestion that lesions with long intramural haematoma without intimal disruption may be associated with worse outcomes. All coronary angiograms were adjudicated by two interventional cardiologists, and classified according to the scheme proposed by the expert panel from the European SCAD scientific statement¹⁰. This categorisation was modified from the original Saw classification endorsed by the American Heart Association SCAD expert consensus panel^{12,11}. It is worth describing in detail the different classifications. Aside from the three standard SCAD angiographic subtypes

(1: multiple radiolucent lumen, 2A: long diffuse narrowing with normal vessel proximal and distal to the stenosis, 2B: long diffuse narrowing that extends to the distal tip of the vessel, and 3: focal-tubular narrowing <20 mm in length mimicking atherosclerosis), there was a proposed additional type 4 to represent total occlusion. This is a controversial categorisation that has not been widely adopted since total occlusion is quite often encountered in SCAD cases and, in order to categorise a total occlusion as SCAD, the characteristics of the lesion proximal to the occlusion have to show convincing evidence of SCAD (either long diffuse narrowing, or presence of multiple lumen), or confirmation by intracoronary imaging or repeat angiography. For instance, in the Canadian SCAD study that included 1,002 dissected arteries, total occlusion was observed in 30.6% of cases, but none of these were categorised as type 4; instead, all occluded arteries were categorised into types 1-3 by core laboratory. Cases of total occlusion that were unclear for SCAD were excluded from our prospective registry⁷.

In this series by Mori, 49.3% had type 2 angiographic SCAD (26.5% type 2A, 22.8% type 2B), 26.8% had type 4, 17.2% had type 1, and 6.6% had type 3. Interestingly, 29.4% (n=89) had TIMI 0 flow, but only 81/89 of these cases were recorded as having type 4 SCAD. A significant proportion of patients (27.8%) had intracoronary imaging. It is unclear why 17/52 (32.6%) type 1 SCAD lesions had intracoronary imaging, since the presence of multiple radiolucent lumen already confirms SCAD diagnosis. In contrast, only 21/81 (28.4%) of type 4 SCAD and 10/20 (50.0%) of type 3 SCAD had intracoronary imaging, when arguably these are the cases where intracoronary imaging will be most useful. Also, a fairly large proportion of patients underwent PCI (33.1%) compared to other contemporary series, yet no differences in outcomes were observed between conservatively managed and revascularisation cases. The authors observed differences in outcomes according to angiographic subtype at 28 days, which were not different at longer-term follow-up. However, the number of events in this retrospective study was small, and the authors had to group subtypes 2A and 3 together in order to conclude that these “circumscribed” contained intramural haematoma were associated with higher composite adverse events. It is unclear why they grouped angiographic types 2A and 3 together, and excluded type 2B, even though all three types mechanistically are due to contained intramural haematoma in the coronary arterial walls. The rational approach would have been to compare dissections that had intimal disruption (i.e., type 1) versus those that were primarily due to intramural haematoma (types 2A, 2B, and 3). Furthermore, the authors did not delineate the type 4 dissections, which arguably also included both types 1 and 2 SCAD per their definition. We suspect that the authors excluded type 2B because of the spuriously lower observed event rates, which is probably attributable to the bias of small sample size, similar to the low event rates observed with type 4. Thus, this artificial subcategorisation into type 2A/3 was not scientifically mechanistically based, and the small sample size and low number of events were confounders to this study’s capacity to correlate angiographic subtypes to outcomes. This

study highlights the need for larger series with greater power to prognosticate from clinical and angiographic variables.

Large strides have been made in gaining greater understanding about SCAD and knowledge translation to the medical and patient communities in the past decade. However, we are still at the tip of the iceberg in our scientific exploration of this disease. Ongoing collaborative efforts in multinational registries and future directions towards large-scale randomised controlled trials to study management strategies are anticipated to drive this voyage forward over the next decade.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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