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EDITORIAL

Spontaneous coronary artery dissection: no longer a rare disease

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This editorial refers to 'Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes', by J. Saw *et al.*, doi:10.1093/eurheartj/ehz007.

Spontaneous coronary artery dissection (SCAD) was, until recently, very much a footnote in the annals of acute cardiovascular disorders. Incorrectly considered a rare disorder, primarily occurring in the peri-partum period or as an unusual complication of connective tissue disorders, it was largely a subject for esoteric case reports rather than serious research. However, the combined impact of higher sensitivity biomarkers of myocardial necrosis, the adoption of early invasive coronary angiography for acute coronary syndromes (ACS), and the introduction of intracoronary imaging has led to a complete reappraisal of this disorder. Led by investigators in the Mayo Clinic, USA and Vancouver, Canada, international groups have presented data from increasingly large observational cohorts of patients with this condition. These studies have demonstrated that SCAD mostly affects young to middle-aged women but that pregnancy-associated SCAD (P-SCAD) makes up only a small fraction (<10%) of the prevalent population, and recognized hereditary connective tissue disorders are rare.[1,2] Furthermore, these studies have shown that SCAD is not a benign condition but has significant reported recurrence (~10% at 3-year follow-up) and major adverse cardiovascular event (MACE) rates.[3–6] Above all, it is increasingly clear that SCAD is not rare but is an important, and still underdiagnosed, cause of ACS, predominantly in women.

In this issue of the *European Heart Journal*, Saw *et al.*[7] report an important further advance, presenting the first large prospectively recruited observational study of SCAD. All previous reported series have been retrospectively recruited and therefore are potentially susceptible to bias. Cases were confirmed by independent core lab assessment of the index coronary angiogram with relatively low rates (7.6%) of intracoronary imaging. Data are presented from 750 patients which, in itself, confirms that SCAD should no longer be considered as being rare. This represents a little under nine patients per centre per year and, given the inevitability of incomplete recruitment, it is perfectly plausible that equivalent sized centres should be expecting at least one new SCAD case presenting per month, thus adding up to a really significant global burden of disease.

Examining the affected population also provides important insights. The reported median age of patients presenting with SCAD has been rising in observational series as recognition of the typical angiographic features improves and pre-conceptions about the affected population abate.[1,2] The fact the reported mean age in this study is 52, with the oldest recruited case over 85 years, has significant implications. First, SCAD should not be considered as a disease restricted to women of menstrual age, and clinicians should be extending their search for potential SCAD cases into an older and post-menopausal population. Secondly, the proposed pathophysiological role of female sex hormones is likely to be more complex than a direct causal effect. This is important as the high female prevalence of SCAD, coupled with the association of some SCAD with the peri-partum period, is frequently used as a justification to caution patients against exogenous sex hormones used, for example, as contraception or hormone replacement therapy.[2] At present, any risk in SCAD survivors associated with contraceptive hormones or hormone replacement therapy remains unknown, but it is interesting to note that only 10% of patients in this cohort were taking any hormone therapy at the time of their SCAD event. Furthermore, this series confirms the previously reported potential association of SCAD with multiparity,[4,8] suggesting perhaps that the vascular consequences of dynamic changes and/or cumulative effects may be more important than hormone exposure *per se*.[9]

SCAD is frequently reported as a disorder which affects primarily women without risk factors for cardiovascular disease. However, this study again confirms that conventional cardiovascular risk factors are not uncommon in patients presenting with SCAD, including hypertension (30.1%), dyslipidaemia (20.3%), and smoking (11.6%), rates which are probably not greatly different from an age- and sex-matched general population. Hence SCAD should be considered in all patients including those with a risk profile for ischaemic heart disease. As reported by Saw *et al.*, emotional stress was recognized as

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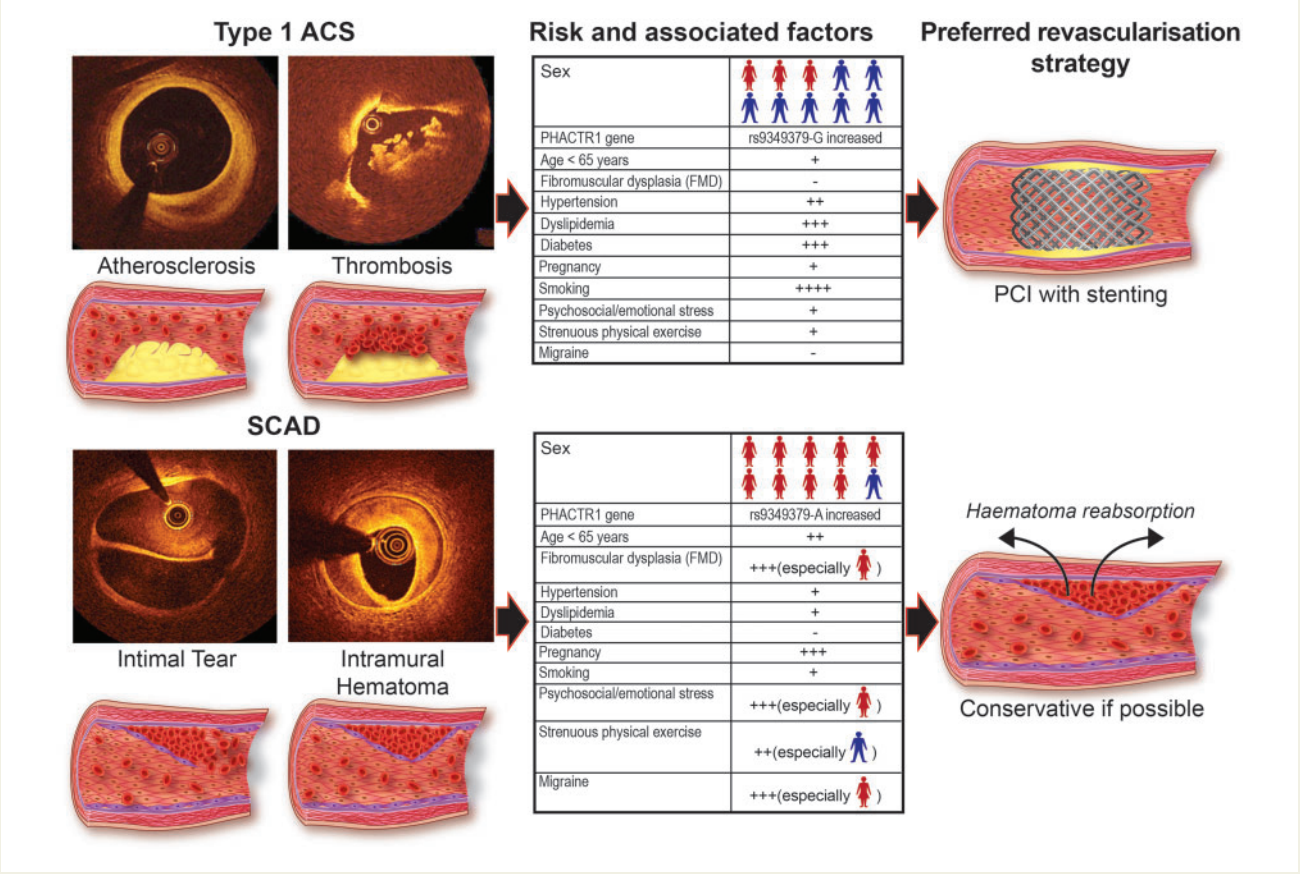

Take home figure Key differences in demographics, associated conditions and management in SCAD compared to Type1 ACS.

an important precipitating factor for SCAD;[7] however, this will need more clarification in future studies. Psychosocial stress may be more involved in variant types of ACS such as SCAD, compared with the classical atherosclerotic type 1 ACS. Gender differences in coping with stress may be another reason why women are relatively more affected by SCAD than men.[9]

A number of other associations have been made with SCAD. These provide intriguing potential pathophysiological insights, although a degree of circumspection about causation remains sensible. It is well established that SCAD is associated with extra-coronary vascular abnormalities in a significant number of cases, including dissections, aneurysms, and, most commonly, fibromuscular dysplasia (FMD).[8,10] The exact prevalence and clinical importance of these abnormalities remain uncertain, with reports from studies where >50% of patients were screened reporting a prevalence of FMD ranging from 41% to 86%. The study of Saw *et al.* reported a lower 31% rate of FMD, increasing to 56.7% in patients with 'complete screening'. The association between SCAD and FMD has recently been confirmed at a genetic level with the demonstration that a common variant on chromosome 6 at the *PHACTR1* locus, rs9349379-A, is a risk locus for both SCAD[11] and FMD,[12] and also cervical artery dissection[13] and migraine[14] (the latter reported by 32.5% of patients in this study). Intriguingly, the minor allele at this locus rs9349379-G is associated with an increased risk of atherosclerotic coronary artery disease and ACS.[15]

Both recent European Position and US Consensus statements emphasize a preference for a conservative ('careful watchful waiting') approach to revascularization where possible, whilst acknowledging that this is not possible in all cases.[1,2] The paper by Saw *et al.* appears to represent a maturation of this management strategy in experienced centres, with >84% of cases managed conservatively. Even in those cases managed with intervention, a minimalist approach was mostly adopted, with only 67 (8.7%) of the 750 patient cohort managed with stenting. It may also be that this overwhelmingly conservative approach was made possible, in part, by increased recognition of angiographically subtler, less extreme forms of the disease, as suggested by what is predominantly a single vessel (86.9%), single segment (74.8%) cohort with low rates of left mainstem involvement (1.5%). As reported in previous series, percutaneous coronary intervention (PCI) outcomes were variable, with 30% deemed 'unsuccessful'. Of note, this group previously reported increased rates of secondary iatrogenic catheter-induced dissections in SCAD, particularly during PCI and where a radial access route was used.[16] In this series, iatrogenic dissection rates occurred at 1.2% which, although not trivial, is lower than previously reported despite the predominant use of a radial route of access. These results may reflect increasing adoption of the cautious technique required when angiography and/or PCI are performed in the setting of SCAD.

Reassuringly, mortality following SCAD is low, with only a single death reported in this series. However, as deaths may be early (or

pre-hospital) and the sickest patients will not be recruited, this is likely to be an underestimate. Thirty-day MACE are reported at 8.8%, with two-thirds of events occurring pre-discharge. In this overwhelmingly conservatively managed population, it is encouraging that only 46 (6.1%) patients presented with recurrent myocardial infarction, 30 occurring during the median 4-day hospital stay, and in only 23 patients (3% of the total) was this due to an extension of dissection. This strongly vindicates the 'conservative if possible' approach and does not suggest that PCI as a strategy to prevent dissection propagation or extension is justified. However, the early accumulation of MACE shown does perhaps support a longer period of inpatient observation for SCAD patients. Clearly longer term follow-up and in particular recurrence rates reported from this series will be awaited with considerable interest. Finally, it is becoming increasingly evident that P-SCAD is a more malignant and high-risk entity. A total of 34 cases are reported in this cohort, and larger focused studies will be needed to provide greater clarity on this important SCAD subgroup.

In summary, it is increasingly clear that SCAD is not rare but is an important and still frequently underdiagnosed cause of ACS, predominantly in women. Its pathophysiology is different from that of conventional atherosclerotic coronary disease and it has a very distinct profile of clinical risks, leading to important differences in the optimal approach to management (such as favouring a conservative approach to revascularization). The initiation of Canadian, US, and European (European Observational Research Programme) observational cohorts, coupled with an international collaborative research effort, promises to continue our rapidly advancing understanding of this condition and further optimize the management and outcomes of SCAD survivors.

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