## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | A nationwide observational study of incidence, management and outcome of spontaneous coronary artery dissection - a report from the Swedish Coronary Angiography and Angioplasty register |
| **AUTHORS** | Wilander, Henrik; Pagonis, Christos; Venetsanos, Dimitrios; Swahn, Eva; Dworeck, Christian; Johnston, Nina; Jonasson, Lena; Kellerth, Thomas; Tornvall, Per; Yndigegn, Troels; Sederholm Lawesson, Sofia |

## VERSION 1 – REVIEW

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| **REVIEWER** | Psaltis, Peter<br>University of Adelaide |
| **REVIEW RETURNED** | 05-Feb-2022 |

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| **GENERAL COMMENTS** | This manuscript describes the demographics, baseline characteristics, management and outcomes of patients with spontaneous coronary dissection from a well-established Swedish registry of coronary angiography cases. The manuscript is clearly written. Its main strengths are that its results are from a nationwide registry, comparison is made to non-SCAD MI cases over the same period and follow-up data are provided for MACE and acute re-angiography. Although the information gained from this study is not particularly novel, it does deal with an increasingly recognised condition for which there are still many important knowledge gaps. While this study doesn't necessarily fill any of these gaps, its findings do contain some unexpected differences compared to other contemporary studies. These include: 1) a higher proportion of males among SCAD cases; 2) SCAD contributing to a lower percentage of MI cases among females <50 yo; 3) a surprising and perhaps alarmingly high rate of attempted PCI to manage SCAD cases; 4) high rates of DAPT and statin use on discharge which were similar to the management of traditional non-SCAD MI cases.<br>The authors emphasise that their study captures a representative and unselected population of SCAD cases. However, I suspect that the first two of these differences reflects significant under-recognition of SCAD in their registry. While angiograms of cases of suspected / diagnosed SCAD were re-evaluated to confirm the diagnosis, this does not address cases in which SCAD was not correctly recognised. This has arguably been the more common and potentially more dangerous issue in real-world practice.<br><br>Although the authors sit on the fence in their discussion around the high rates of PCI use in their study, on the grounds that there is no randomised evidence for or against PCI in SCAD (line 27, page 16), conventional wisdom based on reproducible observational data is that conservative management of SCAD is preferable. |

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| | Similarly, the practice of routinely prescribing DAPT and statins in SCAD cases goes against current recommendations. The study's findings therefore reflect the lack of familiarity that most Cardiologists have had with managing SCAD, especially prior to 2018. I think the authors should emphasise this more as a key take-home message.<br><br>Other specific comments:<br>1) The abstract should provide context about the length of follow-up when reporting outcome results. Similarly, the median (or mean) length of follow-up should be described in the Results section.<br>2) SCAD patients often have recurrent non-ACS chest pain in the first 6-12 months after their index event and this can obviously lead to repeat angiography. It would therefore be helpful to report the median/mean time to re-angiography in both groups.<br>3) Please report the prevalence of fibromuscular dysplasia. If this information is not available, this should be stated as a limitation and should probably be collected in the registry in the future.<br>4) Please report the arterial distribution of SCAD and if possible whether it involved proximal, mid or distal segments of artery. Were there any cases of multivessel SCAD?<br>5) As the absolute number of outcome events in the SCAD group was low, it is not surprising that the authors have not reported predictors of MACE but this should also be stated as a limitation. They should also consider discussing their outcome results in the context of a recent meta-analysis (PMID: 32861717) and data from the European DISCO registry (e.g. PMID 34338759).<br>6) Did you consider performing propensity-matched analysis of outcomes between the SCAD and non-SCAD MI groups (e.g. with matching for age, sex and type of MI).<br>7) Given the possibility that some of the results reflect under-diagnosis of SCAD and lack of familiarity with its recommended management, it might be interesting to compare data by type of hospital (e.g. teaching vs non-teaching, public vs private).<br>8) Table 2 shows that 26 SCAD cases had coronary occlusion, while Table S2 indicates that only 16 cases were classified as Type IV. Please comment.<br>9) In Table 2 the rates of coronary occlusion in both SCAD and non-SCAD groups are much lower than the prevalence of STEMI. Was this because of the use of thrombolytics for some STEMI cases? If so, please report this data for both groups.<br>10) Please modify the following sentence to read correctly: “In SCAD patients with 100% coronary artery occlusion underwent PCI of which 65.5% were treated with stent implantation.” (Line 20, page 11)<br>9) Line 25-26, page 11 is repeated from the paragraph above, but reports a different rate of intracoronary imaging use in non-SCAD MI patients. The previous paragraph states 3.9%, while here it reads 3.3%. Please remove the duplicated information and report the correct rate of IVUS/OCT use. |

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| **REVIEWER** | Souteyrand, Géraud<br>Clermont-Ferrand University Hospital, Cardiology Department |
| **REVIEW RETURNED** | 21-Feb-2022 |

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| **GENERAL COMMENTS** | I've read with interest the manuscript entitled "observational study of incidence, management and outcome of spontaneous coronary artery dissection..." |

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| | The subject is interesting. The authors used data from the Swedish Coronary Angiography and Angioplasty register.<br><br>The patients were included between 2015 and 2017.<br><br>Initially 264 patients were diagnosed with SCAD at 30 centres but eventually only 147 (55%) were validated. The main issue of the study was that an interventional cardiologist in each centre confirmed the diagnosis; it is known that the diagnosis of SCAD on angiography alone is complicated, it is difficult to be certain. This is why a double reading would have been interesting and that the reading was centralised in an expert centre. It would be interesting to see the difference in prevalence between centres: 147 patients in 24 centres. Some centres are less attentive to diagnosis and this could explain the lower incidence.<br><br>Several elements are missing concerning the group of patients with SCAD: which artery was responsible for the SCAD. Which arterial zone is responsible for SCAD? It isn't the same management when the SCAD is proximal or distal in the artery.<br>The rate of STEMI as initial presentation is higher than previous studies: 47% which may explain the high rate of stenting in the SCAD group (40%).<br>In this STEMI population it would have been interesting to compare the delay in care between the two groups.<br><br>It is surprising to see that 80% of the patients with SCAD had DAPT especially in case of hematoma without intimal rupture.<br><br>The discussion is well written but does not add anything new to the existing literature.<br>I'm agree with the comment that a certain underdiagnosis have caused a lower degree of identification of SCAD cases but it should be added in the limit of the study.<br>P13, it is noted that the difference in prevalence could be related to genetic variations vs Japan. But in Eurointervention 2017, P. Motreff et al. found a high prevalence in female MI patients <50 years. You should change this comment and add the publication in the manuscript.<br>P 14 it's written that SCAD type 3 was diagnosed without using OCT/IVUS. But in the definition of type 3, the diagnosis should be confirmed by OCT or IVUS. Please explain.<br>The diagnosis with the angiography is very difficult in a lot of cases without angiographic control or intravascular imaging.<br><br>For the outcome, the follow up in not very long: median follow up is 17.3 months. It's noted that there is a re angiography but we don't know the delay and the indication of the control. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Dr. Peter Psaltis, University of Adelaide
Comments to the Author:

While this study doesn't necessarily fill any of these gaps, its findings do contain some unexpected differences compared to other contemporary studies.
These include:
1) a higher proportion of males among SCAD cases;
A: With the increasing interest and awareness of SCAD, the number of men with SCAD seems to be increasing as well as in our study. The true prevalence of SCAD in men and women is still to be elucidated.
2) SCAD contributing to a lower percentage of MI cases among females <50 yo;
A: Please see point 1. SCAD is still a difficult diagnosis with angiography alone. Without specific knowledge of SCAD this diagnosis may have been missed in premenopausal women.

3) a surprising and perhaps alarmingly high rate of attempted PCI to manage SCAD cases;
A: This reflects also the lack of knowledge among interventional cardiologists prior to 2018 ( publication of ESC SCAD position paper), about this diagnosis, thus treating them as atherosclerotic patients. Alternatively, no data of hemodynamic significance / instability were available.

4) high rates of DAPT and statin use on discharge which were similar to the management of traditional non-SCAD MI cases.
A: See above comments. Poor knowledge of SCAD and thus treating them as atherosclerotic patients. Furthermore there are different guidelines in North America and Europe regarding DAPT in SCAD.

The authors emphasise that their study captures a representative and unselected population of SCAD cases. However, I suspect that the first two of these differences reflects significant under-recognition of SCAD in their registry. While angiograms of cases of suspected / diagnosed SCAD were re-evaluated to confirm the diagnosis, this does not address cases in which SCAD was not correctly recognised. This has arguably been the more common and potentially more dangerous issue in real-world practice.
A: We wholeheartedly agree with Dr. Psaltis here. This holds true for all registry material. We are currently working on a nationwide project to increase the knowledge, awareness and reporting of SCAD in our national quality registry (SCAAR). We plan to evaluate this project through a new set of data up to 2021 from SCAAR.

Although the authors sit on the fence in their discussion around the high rates of PCI use in their study, on the grounds that there is no randomized evidence for or against PCI in SCAD (line 27, page 16), conventional wisdom based on reproducible observational data is that conservative management of SCAD is preferable. Similarly, the practice of routinely prescribing DAPT and statins in SCAD cases goes against current recommendations. The study's findings therefore reflect the lack of familiarity that most Cardiologists have had with managing SCAD, especially prior to 2018. I think the authors should emphasize this more as a key take- home message.
A: We agree to the reviewer’s comment. Data prior to 2018 reflect the lack of familiarity with SCAD diagnosis and treatment. We are working on changing this through RRCTs in Sweden. We emphasized this in the discussion section.
Other specific comments:
1)The abstract should provide context about the length of follow-up when reporting outcome results. Similarly, the median (or mean) length of follow-up should be described in the Results section.
A: We thank you for this valuable comment. It is now added in the abstract and results section.

2) SCAD patients often have recurrent non-ACS chest pain in the first 6-12 months after their index event and this can obviously lead to repeat angiography. It would therefore be helpful to report the

median/mean time to re-angiography in both groups.
A: We thank you for this valuable comment. It is now added in the results section.

3)Please report the prevalence of fibromuscular dysplasia. If this information is not available, this should be stated as a limitation and should probably be collected in the registry in the future.
A: Screening for FMD was not started in Sweden at that time. It is now stated in the limitations. A prospective prevalence study is ongoing.

4) Please report the arterial distribution of SCAD and if possible whether it involved proximal, mid or distal segments of artery. Were there any cases of multivessel SCAD?
A: Segment distribution in SCAAR in angiography alone is not compulsory, therefore it is missing information in many SCAD patients. A segment analysis of SCAD was therefore not done.

5) As the absolute number of outcome events in the SCAD group was low, it is not surprising that the authors have not reported predictors of MACE but this should also be stated as a limitation. They should also consider discussing their outcome results in the context of a recent meta-analysis (PMID: 32861717) and data from the European DISCO registry (e.g. PMID 34338759).
A: We thank the reviewer for making us aware of this meta-analysis. It is now added in the discussion. We deem our results to be in concordance to this study.

6) Did you consider performing propensity-matched analysis of outcomes between the SCAD and non-SCAD MI groups (e.g. with matching for age, sex and type of MI).
A: We did consider it but we thought that it would not add any value to the analysis due to the aforementioned limitations ( small population).

7) Given the possibility that some of the results reflect under-diagnosis of SCAD and lack of familiarity with its recommended management, it might be interesting to compare data by type of hospital (e.g. teaching vs non-teaching, public vs private).
A: Yes, it is an interesting point. Most patients were diagnosed in teaching hospitals (95 individuals out of 147) but no reasonable comparison can be made due to low numbers of recruitment in smaller hospitals and immense selection bias. Furthermore, large regions in Sweden are serviced in out-of office hours by tertiary teaching hospitals making comparisons even more difficult. There are no private PCI centra in Sweden.

8) Table 2 shows that 26 SCAD cases had coronary occlusion, while Table S2 indicates that only 16 cases were classified as Type IV. Please comment.
A: This reflects partly the fact that some lesions were typed other than type IV SCAD but the operator deemed the vessel as functionally occluded (as in e.g. a type IIb SCAD lesion with little contrast staining the distal vessel) and the difficulty in typing SCAD correctly prior to 2018.

9) In Table 2 the rates of coronary occlusion in both SCAD and non-SCAD groups are much lower than the prevalence of STEMI. Was this because of the use of thrombolytics for some STEMI cases? If so, please report this data for both groups.
A: No thrombolytics were administered in our population, all were referred for angiography/PCI. The difference between STEMI rates is probably due to the layout of the registry and the definition / final diagnosis in this group of patients.

10) Please modify the following sentence to read correctly: "In SCAD patients with 100% coronary artery occlusion underwent PCI of which 65.5% were treated with stent implantation." (Line 20, page 11)
A: Thank you for this comment. We rephrased to” Of SCAD patients with total coronary occlusions, 65.5% underwent PCI with at least one stent implanted”

11) Line 25-26, page 11 is repeated from the paragraph above, but reports a different rate of intracoronary imaging use in non-SCAD MI patients. The previous paragraph states 3.9%, while here it reads 3.3%. Please remove the duplicated information and report the correct rate of IVUS/OCT use
A: Thank you for this comment, we now deleted the duplicate sentence. The OCT / IVUS rate in non-SCAD MI was 3.9% ( tab.2.)

Reviewer: 2
Dr. Géraud Souteyrand, Clermont-Ferrand University Hospital
Comments to the Author:
Initially 264 patients were diagnosed with SCAD at 30 centres but eventually only 147 (55%) were validated. The main issue of the study was that an interventional cardiologist in each centre confirmed the diagnosis; it is known that the diagnosis of SCAD on angiography alone is complicated, it is difficult to be certain. This is why a double reading would have been interesting and that the reading was centralised in an expert centre. It would be interesting to see the difference in prevalence between centres: 147 patients in 24 centres. Some centres are less attentive to diagnosis and this could explain the lower incidence.
A: Please see reviewer 1.4. and the revised limitations section.

Several elements are missing concerning the group of patients with SCAD:
which artery was responsible for the SCAD.
A: Please see above comment and the limitations section.

Which arterial zone is responsible for SCAD? It isn't the same management when the SCAD is proximal or distal in the artery.
A: Please see above.

The rate of STEMI as initial presentation is higher than previous studies: 47% which may explain the high rate of stenting in the SCAD group (40%).
A: This is an interesting comment. One explanation could be that non-STEMI SCAD in young women do not lead to an angiogram in the first place. Another explanation could be that STEMI angiograms are more rigorously scrutinized.

In this STEMI population it would have been interesting to compare the delay in care between the two groups.
A: This was not the aim of the study and we do not have this variable from the SCAAR registry.

It is surprising to see that 80% of the patients with SCAD had DAPT especially in case of hematoma without intimal rupture.
A: This is maybe not so surprising as most SCAD patients were treated as atherosclerotic patients prior to 2018. This is illustrated in the recently published meta-analysis by Franke et al ( PMID 32861717) where 84% of patients were treated with DAPT. It is however lower than atherosclerotic patients in Sweden.

I'm agree with the comment that a certain underdiagnosis have caused a lower degree of identification of SCAD cases but it should be added in the limit of the study.
A: Thank you for the comment, it is now added in the limitations section.

P13, it is noted that the difference in prevalence could be related to genetic variations vs Japan. But in Eurointervention 2017, P. Motreff et al. found a high prevalence in female MI patients <50 years. You should change this comment and add the publication in the manuscript.
A: Thank you for the comment. The supposed hypothetical statement about genetic differences with Japan is now discarded.

P 14 it's written that SCAD type 3 was diagnosed without using OCT/IVUS. But in the definition of type 3, the diagnosis should be confirmed by OCT or IVUS. Please explain.
A: This illustrates the difficulty cardiologists have had in typing dissections according to Saw classification. Of course a type III lesion can only be verified with imaging studies.

The diagnosis with the angiography is very difficult in a lot of cases without angiographic control or intravascular imaging.
A: See above comment. It is mentioned in the limitation section.

For the outcome, the follow up in not very long: median follow up is 17.3 months. It's noted that there is a re angiography but we don't know the delay and the indication of the control.
A: We have only considered patients with the need for an acute, unplanned angiography in our study.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Psaltis, Peter<br>University of Adelaide |
| **REVIEW RETURNED** | 11-Apr-2022 |

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| **GENERAL COMMENTS** | I am satisfied that the authors have addressed my comments and that the changes they have made to their manuscript recognises the limitations of their study and provides a more appropriate take-home message. |

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| **REVIEWER** | Souteyrand, Géraud<br>Clermont-Ferrand University Hospital, Cardiology Department |
| **REVIEW RETURNED** | 25-Apr-2022 |

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| **GENERAL COMMENTS** | The authors have improved the manuscript and answered our questions.<br>There are still important limitations to the paper related to the lack of registry data and the technique of reviewing angiograms. |