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A nationwide observational study of incidence, management and outcome of spontaneous coronary artery dissection - a report from the Swedish Coronary Angiography and Angioplasty register

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A nationwide observational study of incidence, management and outcome of spontaneous coronary artery dissection - a report from the Swedish Coronary Angiography and Angioplasty register

Running head: Spontaneous coronary artery dissection (SCAD) in Sweden

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Abstract

Objectives

The aim of this study was to conduct a nationwide all comer description of incidence, contemporary management and outcome in Swedish spontaneous coronary artery dissection (SCAD) patients. The incidence of SCAD as well as the management and outcome of these patients is not well described.

Design

A nationwide observational study.

Participants and Setting

All patients with SCAD registered in the Swedish coronary angiography and angioplasty register (SCAAR) from 2015 to 2017 were included. The index angiographies of patients with registered SCAD were re-evaluated at each centre to confirm the diagnosis. Patients with non-SCAD MI (n=32 601) were used for comparison.

Outcome measures

Outcomes included all-cause mortality, re-infarction or acute coronary re-angiography.

Results

This study found 147 SCAD patients, rendering an incidence of 0.74 per 100.000 per year and a prevalence of 0.43% of all MIs. The average age was 52.9 years, 75.5% were women and 47.6% presented with ST-segment elevation MI. Percutaneous coronary intervention (PCI) was attempted in 40.1% of SCAD patients and 30.6% received stent. The use of anti-thrombotic agents was similar between the groups and there was no difference regarding outcomes, 10.9% vs 13.4%, p=0.75. Mortality was lower in SCAD patients, 2.7% vs 8.0%,

Version: 2021-11-14

p = 0.03, whereas SCAD patients more often underwent acute re-angiography, 9.5% vs 4.6%, p<0.01.

Conclusion

In this nationwide, all comer Swedish study, the overall incidence of SCAD was low, including 25% men which is more and in contrast to previous studies. Compared with non-SCAD MI, SCAD patients were younger, with lower cardiovascular risk burden, yet suffered substantial mortality and morbidity and more frequently underwent acute coronary re-angiography.

Key words

Spontaneous coronary artery dissection (SCAD); ACS/NSTE-ACS; STEMI

Article Summary

Strengths and limitations of this study

- All patients in Sweden considered having SCAD during the study period, and all centers performing invasive coronary angiography are represented.
- All angiographies where SCAD was reported in the SCAAR registry were reviewed and validated by an independent interventional cardiologist.
- All data regarding demographics, management, treatment and in-hospital outcomes are immediately registered on-line, thus limiting recall bias and missing values as these variables are compulsory to register.
- Limitations include possible heterogeneity in the confirmation of SCAD diagnosis as the study did not include a core-lab.

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Version: 2021-11-14

Introduction

Spontaneous coronary artery dissection (SCAD) has been reported as the underlying cause of myocardial infarction (MI) in 0.2-4% of all cases with an inherent risk of sudden cardiac death.(1, 2) The dissection occurs independently of atherosclerosis causing coronary flow obstruction and acute myocardial ischemia.(3) The majority of SCAD patients are women between 44-53 years.(4, 5) The presence of conventional cardiovascular risk factors is low.(2, 6) Instead, the etiology of SCAD is multifactorial and often includes a pre-existing arteriopathy.(2, 7, 8)

SCAD presenting as Saw type 1 is an angiographic diagnosis, but as SCAD type 3 mimics atherosclerotic coronary artery disease (CAD) and type 2 is difficult to diagnose on angiography, clinical awareness, a high level of suspicion and sometimes intravascular imaging such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) in these cases is needed.(6, 7) However, these procedures may lead to propagation of the dissection as guidewires can enter the false lumen.(9, 10)

Percutaneous coronary intervention (PCI) also poses a risk of extending the dissection and carries a risk of stent malapposition subsequent to resorption of the intramural hematoma.(1, 4, 5, 9, 11, 12) Additionally, observational data indicate spontaneous healing within days to months after conservative treatment of SCAD.(1, 4, 13) Hence, current recommendation emphasises conservative treatment of patients without ongoing large areas of ischemia or hemodynamic instability.

The absence of randomised controlled trials (RCT) leaves current guidelines based on expert opinion. While SCAD patients treated by PCI should receive standard dual anti-platelet therapy (DAPT) the support for anti-platelet therapy in conservatively managed SCAD is lacking. Long term mortality after SCAD has been reported to be low with survival rates

Version: 2021-11-14

between 92-100% after 3-6 years follow up.(4, 14) On the other hand SCAD recurrence has been reported in 10-17% during 3-4 years of follow up.(12, 15)

Although better recognised recently,(16-18) SCAD still remains insufficiently studied as there are no nationwide reports on SCAD MIs relative to type 1 MIs, registered in the same period. Thus, the aim was to study a Swedish all-comer MI population undergoing coronary angiography, describing incidence, prevalence, medical and invasive management and cardiovascular outcomes of SCAD compared with non-SCAD MI.

Method

Study population

This was a retrospective analysis of prospectively collected data using the Swedish coronary angiography and angioplasty registry (SCAAR) (19). Between 17th of December 2015 and 30th of December 2017 all consecutive patients with recorded SCAD, were identified using the SCAD variable launched in SCAAR on 15th of December 2015. Patients with non-SCAD MI who underwent coronary angiography during the same time period were used for comparison.

SCAAR registry

The registry has previously been described, and covers 100% of patients undergoing coronary angiography and PCI in Sweden. Data on baseline characteristics, medical history, procedural characteristics and in-hospital complications are prospectively collected. SCAAR is a part of the Swedish Web-system for Enhancement and Development of Evidence based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). (19)

Ongoing medication on arrival and at discharge were obtained by merging SCAAR with the Swedish register of information and knowledge about Swedish heart intensive care admissions (RIKS-HIA), another part of SWEDEHEART.

Version: 2021-11-14

Angiographic SCAD diagnosis

All index angiographies of patients with SCAD were re-evaluated by an independent interventional cardiologist at each center to confirm the diagnosis. Patients without confirmed SCAD were excluded. SCAD was defined according to the Saw angiographic classification of SCAD. (Supplementary Table 1) Coronary artery dissections evaluated as secondary to atherosclerotic plaque rupture or iatrogenic dissections were excluded.

Definition of outcomes and complications

The primary outcomes of this study were all-cause mortality, myocardial re-infarction, and acute invasive coronary re-angiography. Recurrent MI was defined as readmission according to the International Classification of Diseases (ICD) codes I21 and I22. Acute re-angiography was defined as an unplanned new coronary angiography after the index event. Information about all-cause mortality and MI were obtained by merging SCAAR with the national population registry and RIKS-HIA, respectively. Data about re-angiography and PCI were derived from SCAAR. Follow up for death and MI was available until June 2018 and for coronary re-angiography until January 2018.

Ethics

All patients were informed of their participation in the SCAAR registry, and their possibility to withdraw their consent at any time. Anyhow, according to Swedish regulations, written informed consent is not required for registration in national quality registries such as SCAAR. Permission for the study was obtained from the regional Ethical Review Board, Linkoping, Sweden (Dnr 2018/122-31), and complied with the Declaration of Helsinki. Patient data were anonymised to protect integrity.

Statistical analysis

Data are presented as numbers and percentages, mean ± standard deviations, or median with interquartile range, as appropriate. Comparisons of continuous variables were performed with the Student T-test, when normal distribution was present, otherwise the Mann Whitney U test

Version: 2021-11-14

was used. Comparison of categorical variables between groups was performed using the Chi^2 test. Rate of cardiovascular events over time is presented using Kaplan-Meier curves and outcome comparisons were performed using the log-rank tests. Any p-value <0.05 is considered to indicate statistical significance. The overall proportion of missing data was low, <2.5% of patients regardless of variable, except for smoking status which was missing in 7.2% of patients with non-SCAD MI. IBM SPSS statistics version 25 was used.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Patient characteristics

In total, 264 patients from 30 centers were identified in SCAAR with an initial SCAD diagnosis alongside 32 601 patients with non-SCAD MI. After re-evaluating angiograms of all patients with registered definite or suspected SCAD, the diagnosis of definite SCAD was confirmed in 147 patients from 24 centers. According to Statistics Sweden, the average population in Sweden in the years 2015-2017 was 9 985 629 individuals, rendering an incidence of SCAD at 0.74 per 100.000 per year and a prevalence of 0.43% of all MI cases undergoing coronary angiography in Sweden at the same time. The prevalence of SCAD was 2.2% in the MI population <50 years, (7.3% and 0.8% in women and men respectively). With a mean age of 52.9 years, SCAD patients were younger than patients with non-SCAD MI, 68.5 year (p<0.01). The SCAD group consisted of 75.5% women compared to 31.9% of the non-SCAD MI group. The prevalence of cardiovascular risk factors, use of acetylsalicylic

Version: 2021-11-14

acid (ASA), statins and anti-hypertensive medications on admission was lower in the SCAD group. (Table 1)

Table 1. Baseline characteristics in SCAD and non-SCAD myocardial infarction (MI)

	SCAD MI n=147 n (%)	Non-SCAD MI n=32601 n (%)	p-value
Age	52.9 ±12.2	68.5 ±11.8	<0.01
Female gender	111 (75.5)	10391 (31.9)	<0.01
Diabetes	3 (2.0)	6921 (21.4)	<0.01
Hypertension[1]	39 (26.5)	19070 (59.4)	<0.01
Hyperlipidemia[2]	20 (13.7)	9125 (30.4)	<0.01
Smoking history[3]	56 (38.1)	17599 (58.1)	<0.01
Previous MI	16 (10.9)	6733 (21.1)	<0.01
Previous CABG	0	1996 (6.1)	<0.01
Previous PCI	6 (4.1)	5482 (16.8)	<0.01
ACE-I or ARBs	26 (17.7)	11904 (36.5)	<0.01
Beta-blockers	25 (17.1)	10107 (33.7)	<0.01
ASA	27 (18.5)	8577 (28.6)	<0.01
$P2Y_{12}$-inhibitor	4 (2.7)	1642 (5.5)	0.15
DAPT	3 (2.1)	951 (3.2)	0.44
OAC	7 (4.8)	2426 (7.6)	0.21
Statins	20 (13.7)	9125 (30.4)	<0.01

ACE-I = Angiotensin Converting Enzyme Inhibitor, ARB= Angiotensin Receptor Blocker, ASA = Acetyl Salicylic Acid, CABG= Coronary Artery Bypass Graft Surgery, DAPT= Dual Antiplatelet Therapy, MI= Myocardial Infarction, OAC= Oral Anticoagulants, PCI= Percutaneous Coronary Intervention, SCAD= Spontaneous Coronary Artery Dissection. [1]Anti-hypertensive treatment on admission. [2]Treatment with lipid lowering agents on admission. [3]Active or previous smoking history.

Procedural characteristics

SCAD patients more often presented with STEMI when compared to non-SCAD MI patients, 47.6% and 39.3%, respectively (p<0.01). Coronary artery occlusion was found in 17.7% of

Version: 2021-11-14

SCAD patients and 23.8% of non-SCAD MI patients, p=0.08. (Table 2) Coronary artery atherosclerosis was reported in 17 (11.6%) SCAD patients.

Type 1 dissection was found in 12.2%, type 2A/2B dissection in 72.8%, type 3 dissection in 4,1% and type 4 in 10.9% of SCAD patients (Figure 1). Intracoronary imaging, OCT/IVUS, was used in 24.5% of SCAD patients and in 3.9% of non-SCAD MI patients.

PCI was attempted in 40.1% of SCAD patients and 30.6% received stent. In non-SCAD MI patients corresponding figures were 70.9% and 65.8%, respectively.

In SCAD patients with 100% coronary artery occlusion underwent PCI of which 65.5% were treated with stent implantation. Patients with non-occlusive SCAD were treated with stent implantation in 23% of cases. Intracoronary imaging was used in 24.5 % of SCAD-procedures compared with 3.3% in non-SCAD MI. The general success of PCI was 86.4% in the SCAD group compared to 94.8% in the non-SCAD MI population, p<0.01. (Table 2)

Table 2. Coronary angiography, invasive and medical management in SCAD and non-SCAD myocardial infarction (MI)

	SCAD n=147 n (%)	Non-SCAD MI n=32601 n (%)	p-value
Coronary angiography, findings and procedures			
STEMI	70 (47.6)	12823 (39.3)	<0.01
Coronary artery occlusion	26 (17.7)	7601 (23.8)	0.08
Conservative management	88 (59.9)	9493 (29.1)	<0.01
Attempted PCI	59 (40.1)	23108 (70.9)	<0.01
PCI with stent	45 (30.6)	21455 (65.8)	<0.01
OCT/IVUS	36 (24.5)	1260 (3.9)	<0.01
General success*	51 (86.4)	21913 (94.8)	<0.01
Medical therapy at discharge			
ACE-I or ARBs	87 (59.2)	24187 (74.2)	<0.01
Beta-blockers	118 (81.9)	25370 (86.0)	0.16
ASA	134 (93.1)	26522 (89.9)	0.21
ASA only	17 (11.6)	3096 (9.5)	0.39
$P2Y_{12}$-inhibitor	123 (85.4)	24871 (84.3)	0.72
DAPT	117 (81.3)	23418 (79.4)	0.59
OAC	13 (8.8)	3935 (12.2)	0.22
Statins	110 (76.4)	27036 (91.7)	<0.01

ACE-I= Angiotensin Converting Enzyme Inhibitor, ASA= Acetylsalicylic Acid, ARB= Angiotensin Receptor Blocker, DAPT= Dual Antiplatelet Therapy, MI= Myocardial Infarction, OAC= Oral Anticoagulant, OCT/IVUS= Optical Coherence Tomography/Intravascular Ultrasound, PCI= Percutaneous Coronary Intervention, SCAD= Spontaneous Coronary Artery Dissection, STEMI= ST-segment Elevation Myocardial Infarction, *Subjective assessment by the operator. The operator has reached the main aim of the treatment.

Management stratified by type of dissection is presented in Supplementary Table 2.

Inpatient care time and medical treatment at discharge

There was no difference in days of hospitalisation during index event between the two groups, with a median of 4 days, p=0.93.

The use of betablockers, ASA, $P2Y_{12}$-inhibitors, DAPT and oral anticoagulants (OACs) was similar between the groups at discharge. SCAD patients received DAPT in 81.3% while 11.6% received ASA only and 2.7% received no antiplatelet therapy. Non-SCAD MI patients received more often ACE-I/ARBs and statins at discharge, yet statins were prescribed in 76.4% of SCAD cases. (Table 2, Figure 2)

Outcomes

There was no difference in rate of combined outcomes between the SCAD and the non-SCAD MI groups (10.9 and 13.4%, p=0.75). (Table 3, Figure 3)

Table 3. Outcome in SCAD and non-SCAD myocardial infarction

	SCAD MI n=147 n (%)	Non-SCAD MI n=32601 n (%)	p-value
Death	4 (2.7)	3099 (9.7)	<0.01
MI	3 (2.0)	1424 (4.4)	0.20
Acute coronary re-angiography after discharge	14 (9.5)	1495 (4.6)	<0.01
MI= Myocardial Infarction, SCAD= Spontaneous Coronary Artery Dissection,			

Version: 2021-11-14

Median number of days to outcomes was 10 for SCAD and 25 for non-SCAD MI. The rate of all-cause mortality in SCAD (2.7%) was lower when compared to the non-SCAD MI population (9.7%) (p<0.01). There was no difference in the rate of re-infarction between the SCAD (2.0%) and the non-SCAD MI population (4.4%) (p=0.20). Median number of days until re-infarction in SCAD patients was 37 days. The SCAD population was more often subject to acute re-angiography after the index event (9.5%) than the non-SCAD MI population (4.6%) (p<0.01). (Table 3) Urgent PCI was attempted in 5 SCAD patients. (Supplementary Tables 3 and 4).

Discussion

In this study with 100% nationwide coverage of MI patients undergoing coronary angiography during a two year period we found an incidence of SCAD at 0.74 cases per 100.000 inhabitants per year and a SCAD prevalence of 0.43% of all MI cases in Sweden at the time. The prevalence of SCAD in the MI population <50 years was 2.2% and 7.3% of MI cases in women <50 years. We found an equally high rate of combined outcomes and recurrent MI in the two MI groups whereas SCAD patients were more often subject to acute coronary re-angiography. Although 59.9% were treated conservatively without PCI or CABG, 81.3% of SCAD patients were discharged with DAPT.

Epidemiology

While the prevalence of SCAD was lower than most other studies have suggested, we found a higher prevalence of SCAD than previously published multicenter studies. (20-22) An older study of 32 869 patients from 3 centers in western Denmark identified a SCAD prevalence of

Version: 2021-11-14

0.2% during 8 years whereas a Japanese study of 20 195 MI patients collected in 20 centers during 13 years identified a SCAD prevalence of 0.31% (20-22) The higher prevalence in our cohort may be explained by the increasing knowledge of SCAD and possible genetic differences between the Swedish and Japanese populations. In addition, we did not exclude patients with angiographic signs of atherosclerosis in other than SCAD vessels. On the other hand, when comparing with smaller single center studies, the prevalence in our cohort is lower. This might be attributed to the relatively new SCAD variable in SCAAR with an increasing learning curve among interventionists to recognise and report all types of SCAD in the SCAAR registry. Thus, a certain underdiagnosis may have caused a lower degree of identification of SCAD cases than in centers with special interest in SCAD.

We also found a lower prevalence of SCAD in female MI patients <50 years (7.3%) compared to previous studies. Four studies have reported a SCAD prevalence of 23-36% in women below 50-60 years with MI. Three of these are small single center studies including ≤ 20 SCAD cases less than 60 years. (1, 20, 21) The fourth by Nakashima et. al. reported a SCAD prevalence of 35% in women <50 years with MI. (11) This is in contrast to our findings and we speculate it to be related to genetic variations and a low prevalence of CAD in Japan.

Risk factors

Our results are in line with previous studies showing that SCAD predominantly affects middle-aged women with a low prevalence of cardiovascular risk factors and ongoing cardiovascular medications.(1, 2, 4, 9, 11, 12, 14, 18, 20) Interestingly, 10% of SCAD cases included in our study had suffered a previous MI. This may be explained by SCAD recurrency as we do not know if the indexed SCAD occasion was the first. Rate of recurrency has been described to be between 4.7-17% in 2-4 years which aligns with our findings. (11,

Version: 2021-11-14

12, 14) Other possible explanations are inclusion of patients with concurrent atherosclerosis in other coronary segments than the one affected by SCAD.

Sex

Our SCAD population included 25% men which is in contrast to previous studies - in particular to those where SCAD patients with atherosclerosis have been excluded.(1, 9, 11) However, there are studies with a proportion of male patients between 23% and 46.2%.(21, 22) A consequence of excluding all SCAD patients with any atherosclerosis is the selection of younger and female patients, with a low burden of concomitant co-morbidity. When describing findings from imaging, genetic or proteomic studies there could be a rationale to select patients with a clear-cut SCAD diagnosis. On the other hand, when describing incidence, prevalence, management and prognosis, it is of great importance not to introduce a selection bias by excluding patients with concomitant atherosclerotic manifestations. The current study included all patients with SCAD unless iatrogenic or due to plaque rupture and hence describes the entire SCAD population without selection. Our results indicate that also men are, to a larger extent than previously thought, affected by SCAD, and that the diagnosis should not be overlooked but sought after in these patients too.

Angiography and intervention

Type 2 dissection was the most common angiographic manifestation, in accordance with previous studies, followed by type 1, however only seen in 12.2% as opposed to 29-55% in previous reports. Meanwhile, the prevalence of type 3 was similar between this and other studies.(1, 4, 9, 11) This indicates that intimal flap appearance and dual lumen sign is less prevalent than previously suggested, probably due to increasing recognition of non-classical appearance of SCAD. Although intravascular imaging was more widely used in SCAD patients, a majority of type 3 and 4 SCAD cases were diagnosed without using OCT/IVUS.

As type 3 is defined as angiographically indistinguishable from atherosclerotic coronary artery disease, diagnosing type 3 without intravascular imaging is a limitation in this study.

There are several feasible reasons for this, including technical difficulties in the case of distal occlusions or ignorance of its necessity. In addition, the diagnosis of SCAD mimicking CAD does not always require intravascular imaging but can be made with enough experience without arduous catheterisation.

SCAD patients underwent PCI and stenting less frequently at the index event than non-SCAD MI patients, although PCI was attempted in 40% of cases and 30% received stents. Other retrospective studies of SCAD patients have reported revascularisation rates between 12-56%.(4, 5, 9, 11, 23) As there are no RCTs describing optimal management, we cannot comment on over- or undertreatment. Nor do we have information regarding the clinical circumstances underlying choice of treatment e.g., PCI on vital indication in hemodynamically unstable patients.

Medication

We found the medication at discharge to be remarkably similar in patients with SCAD and non-SCAD MI, including the use of ASA, $P2Y_{12}$-inhibitors and DAPT. This might reflect adherence to current guidelines for ACS in the absence of SCAD specific evidence. (6, 7) In the current study 80% of SCAD patients were treated with betablockers, which has been proposed to be beneficial.(15) In a retrospective study of 327 patients the use of betablockers was associated with a lower risk of recurrent SCAD and this therapy could therefore be considered. (6, 7) The prescription rate of statins was high in SCAD patients, despite not being recommended. (6, 7)

Version: 2021-11-14

Outcomes

The overall rate of outcomes did not differ between SCAD and non-SCAD MI. However, all-cause mortality was lower in SCAD, yet the rate of recurrent MI was equal. Furthermore, SCAD patients were more often subject to acute coronary re-angiography after the index event, 9.5%. This is evidence of significant morbidity in SCAD, especially as age and cardiovascular risk factors have not been adjusted for, due to the relatively small study population with SCAD. In 3 recently published European SCAD-studies (16-18) the unplanned re-angiography was 4%, 8.5% and 5.3% respectively. The present study found a death rate of 2.7% after a median follow-up of 17.3 months indicating a higher mortality than in previous studies. This could be caused by inclusion of a more representative and unselected population of SCAD patients.

Although recurrent MI was equal between the two groups, our 2% recurrency rate is lower than previously described, varying between 4.8-12% per year.(11, 15) SCAD recurrency has been reported at 4.7-17% in 22-47 months. (11, 12, 14) The discrepancy between our study and the American and Canadian series is however small and may be due to different lengths of follow-up as adverse events may not be evenly distributed in time. (12, 15)

The cause of the high rate of acute, unplanned coronary re-angiography after the index event is not known to us and is not explained by recurrent MI or need for revascularisation as PCI was attempted in only 5/14 acute coronary re-angiographies. Further studies are needed to elucidate this, although it is plausible that a high prevalence of recurrent angina and difficulties in chest pain risk assessment could be contributing factors.

Conclusion

Version: 2021-11-14

SCAD patients were comparatively young and previously healthy, yet suffered substantial mortality and morbidity and are frequently subject to acute coronary re-angiography and its accompanying risks. As both incidence and prevalence are low, data highlight the careful need of diagnostic awareness in both men and women and in patients with co-existing atherosclerotic coronary artery disease.

Author statement

H Wilander, S Sederholm Lawesson, D Venetsanos and E Swahn are responsible for the conception and design of the study, have full access to all data, analysed and interpreted the data and drafted the manuscript. C Pagonis gathered the PCI data, critically revised the manuscript and added important intellectual content. C Dworeck, L Jonasson, N Johnston, T Kellerth, P Tornvall and T Yndigegn critically revised the manuscript and added important intellectual content.

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Impact on daily practice

As the knowledge is very scarce regarding SCAD-patients, a nationwide study on all-comers like this, has the potential to be used as a basis for changed routines regarding the handling of SCAD patients and also for new prospective randomised clinical trials challenging the current handling and treatment of these patients.

Disclosure

The Authors declare that there are no conflicts of interest.

Version: 2021-11-14

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Version: 2021-11-14

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Version: 2021-11-14

Figure legends

Figure 1. **Distribution of SCAD subtypes.**

Figure 2. **Medical therapy at discharge.**

Figure 3. **Outcomes in SCAD and non-SCAD MI.**

Figure 1.

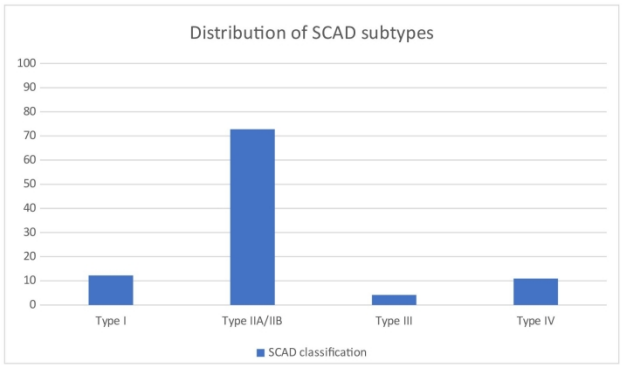

Figure 1

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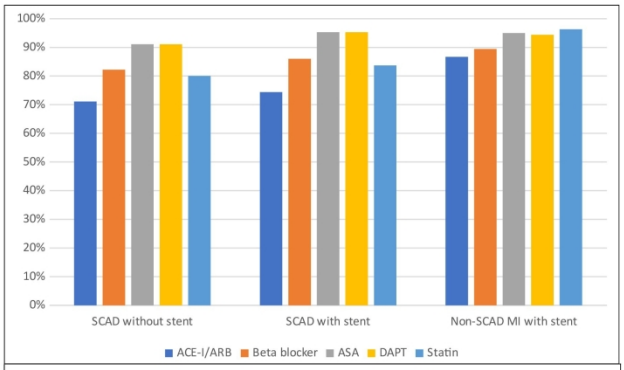
Figure 2.

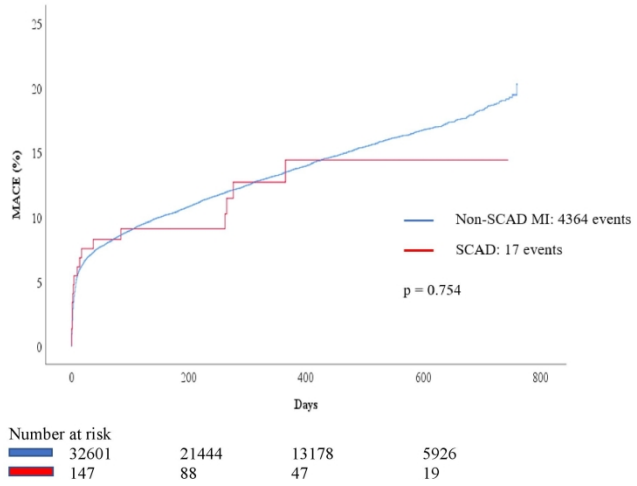


SCAD = Spontaneous Coronary Artery Dissection, MI = Myocardial Infarction, ACE-I = Angiotensin Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ASA = Acetylsalicylic Acid, DAPT = Dual Antiplatelet Therapy.

Figure 2

209x297mm (300 x 300 DPI)

Figure 3.



MACE = Major Adverse Cardiac Events, SCAD = Spontaneous Coronary Artery Dissection, MI = Myocardial Infarction.

Figure 3

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SweSCAD: Supplementary tables and figures

Supplementary Table 1. Saw angiographic classification of SCAD

	Classification
SCAD type 1	The classical angiographic radiolucent ‘flap’ and linear double lumen.
SCAD type 2a/2b	A long diffuse and smooth stenosis predominantly located in mid-to-distal segments, and classical signs of a dissection as in Type 1 are missing; Type 2a: Distal vessel normal; Type 2b: The stenosis extends angiographically to the end of the vessel.
SCAD type 3	Angiographically indistinguishable from a focal atherosclerotic stenosis requiring diagnostic confirmation by OCT or IVUS.
SCAD type 4	Total occlusion. The diagnosis established once coronary flow is re-established or inferred by subsequent vessel healing and the exclusion of an embolic cause.

Supplementary Table 2. Coronary angiography and invasive management in SCAD subtypes

	Saw Classification (index event)	I n=18 (%)	IIA/IIB n=107 (%)	III n=6 (%)	IV n=16 (%)
Diagnostic features	STEMI	7 (38.9)	47 (43.9)	5 (83.3)	11 (68.8)
	OCT/IVUS used	4 (22.2)	26 (24.3)	2 (33.3)	4 (25.0)
Invasive management	Conservative management	13 (72.2)	67 (62.6)	5 (83.3)	3 (18.8)
	Attempted PCI	5 (27.8)	40 (37.4)	1 (16.7)	13 (81.3)
	PCI with stent	5 (27.8)	31 (29.0)	1 (16.7)	8 (50.0)
	General success*	4 (80)	35 (87.5)	1 (100%)	11 (84.6)

MI= Myocardial Infarction, OCT/IVUS= Optical Coherence Tomography / IntraVascular UltraSound, PCI= Percutaneous Coronary Intervention, SCAD= Spontaneous Coronary Artery Dissection, STEMI= ST-segment Elevation Myocardial Infarction.
*Subjective assessment by the operator. The operator has reached the main aim of the treatment.

Supplementary Table 3. Outcome in SCAD subtypes

	I n=18 (%)	IIA/IIB n=107 (%)	III n=6 (%)	IV n=16 (%)
Death	2 (11.1)	0 (0)	0 (0)	2 (12.5)
MI	0 (0)	3 (2.8)	0 (0)	0 (0)
Acute coronary re-angiography	1 (5.5)	10 (9.3)	1 (16.7)	2 (12.5)
MI = Myocardial Infarction, SCAD = Spontaneous Coronary Artery Dissection,				

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9 NA NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

A nationwide observational study of incidence, management and outcome of spontaneous coronary artery dissection - a report from the Swedish Coronary Angiography and Angioplasty register

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A nationwide observational study of incidence, management and outcome of spontaneous coronary artery dissection - a report from the Swedish Coronary Angiography and Angioplasty register

Running head: Spontaneous coronary artery dissection (SCAD) in Sweden

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Abstract

Objectives

The aim of this study was to conduct a nationwide all comer description of incidence, contemporary management and outcome in Swedish spontaneous coronary artery dissection (SCAD) patients. The incidence of SCAD as well as the management and outcome of these patients is not well described.

Design

A nationwide observational study.

Participants and Setting

All patients with SCAD registered in the Swedish coronary angiography and angioplasty register (SCAAR) from 2015 to 2017 were included. The index angiographies of patients with registered SCAD were re-evaluated at each centre to confirm the diagnosis. Patients with non-SCAD MI (n=32 601) were used for comparison.

Outcome measures

Outcomes included all-cause mortality, re-infarction or acute coronary re-angiography.

Results

This study found 147 SCAD patients, rendering an incidence of 0.74 per 100.000 per year and a prevalence of 0.43% of all MIs. The average age was 52.9 years, 75.5% were women and 47.6% presented with ST-segment elevation MI. Median follow up time for MACE was 17.3 months. Percutaneous coronary intervention (PCI) was attempted in 40.1% of SCAD patients and 30.6% received stent. The use of anti-thrombotic agents was similar between the groups and there was no difference regarding outcomes, 10.9% vs 13.4%, p=0.75. Mortality was lower in SCAD patients, 2.7% vs 8.0%,

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p = 0.03, whereas SCAD patients more often underwent acute re-angiography, 9.5% vs 4.6%, p<0.01.

Conclusion

In this nationwide, all comer Swedish study, the overall incidence of SCAD was low, including 25% men which is more and in contrast to previous studies. Compared with non-SCAD MI, SCAD patients were younger, with lower cardiovascular risk burden, yet suffered substantial mortality and morbidity and more frequently underwent acute coronary re-angiography.

Key words

Spontaneous coronary artery dissection (SCAD); ACS/NSTE-ACS; STEMI

Article Summary

Strengths and limitations of this study

- All patients in Sweden considered having SCAD during the study period, and all centers performing invasive coronary angiography are represented.
- All angiographies where SCAD was reported in the SCAAR registry were reviewed and validated by an independent interventional cardiologist.
- All data regarding demographics, management, treatment and in-hospital outcomes are immediately registered on-line, thus limiting recall bias and missing values as these variables are compulsory to register.
- Limitations include possible heterogeneity in the confirmation of SCAD diagnosis as the study did not include a core-lab.

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Version: 2021-11-14

Introduction

Spontaneous coronary artery dissection (SCAD) has been reported as the underlying cause of myocardial infarction (MI) in 0.2-4% of all cases with an inherent risk of sudden cardiac death.(1, 2) The dissection occurs independently of atherosclerosis causing coronary flow obstruction and acute myocardial ischemia.(3) The majority of SCAD patients are women between 44-53 years.(4, 5) The presence of conventional cardiovascular risk factors is low.(2, 6) Instead, the etiology of SCAD is multifactorial and often includes a pre-existing arteriopathy.(2, 7, 8)

SCAD presenting as Saw type 1 is an angiographic diagnosis, but as SCAD type 3 mimics atherosclerotic coronary artery disease (CAD) and type 2 is difficult to diagnose on angiography, clinical awareness, a high level of suspicion and sometimes intravascular imaging such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT) in these cases is needed.(6, 7) However, these procedures may lead to propagation of the dissection as guidewires can enter the false lumen.(9, 10)

Percutaneous coronary intervention (PCI) also poses a risk of extending the dissection and carries a risk of stent malapposition subsequent to resorption of the intramural hematoma.(1, 4, 5, 9, 11, 12) Additionally, observational data indicate spontaneous healing within days to months after conservative treatment of SCAD.(1, 4, 13) Hence, current recommendation emphasises conservative treatment of patients without ongoing large areas of ischemia or hemodynamic instability.

The absence of randomised controlled trials (RCT) leaves current guidelines based on expert opinion. While SCAD patients treated by PCI should receive standard dual anti-platelet therapy (DAPT) the support for anti-platelet therapy in conservatively managed SCAD is lacking. Long term mortality after SCAD has been reported to be low with survival rates

Version: 2021-11-14

between 92-100% after 3-6 years follow up.(4, 14) On the other hand SCAD recurrence has been reported in 10-17% during 3-4 years of follow up.(12, 15)

Although better recognised recently,(16-18) SCAD still remains insufficiently studied as there are no nationwide reports on SCAD MIs relative to type 1 MIs, registered in the same period. Thus, the aim was to study a Swedish all-comer MI population undergoing coronary angiography, describing incidence, prevalence, medical and invasive management and cardiovascular outcomes of SCAD compared with non-SCAD MI.

Method

Study population

This was a retrospective analysis of prospectively collected data using the Swedish coronary angiography and angioplasty registry (SCAAR) (19). Between 17th of December 2015 and 30th of December 2017 all consecutive patients with recorded SCAD, were identified using the SCAD variable launched in SCAAR on 15th of December 2015. Patients with non-SCAD MI who underwent coronary angiography during the same time period were used for comparison.

SCAAR registry

The registry has previously been described, and covers 100% of patients undergoing coronary angiography and PCI in Sweden. Data on baseline characteristics, medical history, procedural characteristics and in-hospital complications are prospectively collected. SCAAR is a part of the Swedish Web-system for Enhancement and Development of Evidence based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). (19)

Ongoing medication on arrival and at discharge were obtained by merging SCAAR with the Swedish register of information and knowledge about Swedish heart intensive care admissions (RIKS-HIA), another part of SWEDEHEART.

Version: 2021-11-14

Angiographic SCAD diagnosis

All index angiographies of patients with SCAD were re-evaluated by an independent interventional cardiologist at each center to confirm the diagnosis. Patients without confirmed SCAD were excluded. SCAD was defined according to the Saw angiographic classification of SCAD. (Supplementary Table 1) Coronary artery dissections evaluated as secondary to atherosclerotic plaque rupture or iatrogenic dissections were excluded.

Definition of outcomes and complications

The primary outcomes of this study were all-cause mortality, myocardial re-infarction, and acute invasive coronary re-angiography. Recurrent MI was defined as readmission according to the International Classification of Diseases (ICD) codes I21 and I22. Acute re-angiography was defined as an unplanned new coronary angiography after the index event. Information about all-cause mortality and MI were obtained by merging SCAAR with the national population registry and RIKS-HIA, respectively. Data about re-angiography and PCI were derived from SCAAR. Follow up for death and MI was available until June 2018 and for coronary re-angiography until January 2018.

Ethics

All patients were informed of their participation in the SCAAR registry, and their possibility to withdraw their consent at any time. Anyhow, according to Swedish regulations, written informed consent is not required for registration in national quality registries such as SCAAR. Permission for the study was obtained from the regional Ethical Review Board, Linkoping, Sweden (Dnr 2018/122-31), and complied with the Declaration of Helsinki. Patient data were anonymised to protect integrity.

Statistical analysis

Data are presented as numbers and percentages, mean ± standard deviations, or median with interquartile range, as appropriate. Comparisons of continuous variables were performed with the Student T-test, when normal distribution was present, otherwise the Mann Whitney U test

Version: 2021-11-14

was used. Comparison of categorical variables between groups was performed using the Chi^2 test. Rate of cardiovascular events over time is presented using Kaplan-Meier curves and outcome comparisons were performed using the log-rank tests. Any p-value <0.05 is considered to indicate statistical significance. The overall proportion of missing data was low, <2.5% of patients regardless of variable, except for smoking status which was missing in 7.2% of patients with non-SCAD MI. IBM SPSS statistics version 25 was used.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Patient characteristics

In total, 264 patients from 30 centers were identified in SCAAR with an initial SCAD diagnosis alongside 32 601 patients with non-SCAD MI. After re-evaluating angiograms of all patients with registered definite or suspected SCAD, the diagnosis of definite SCAD was confirmed in 147 patients from 24 centers. According to Statistics Sweden, the average population in Sweden in the years 2015-2017 was 9 985 629 individuals, rendering an incidence of SCAD at 0.74 per 100.000 per year and a prevalence of 0.43% of all MI cases undergoing coronary angiography in Sweden at the same time. The prevalence of SCAD was 2.2% in the MI population <50 years, (7.3% and 0.8% in women and men respectively). With a mean age of 52.9 years, SCAD patients were younger than patients with non-SCAD MI, 68.5 year (p<0.01). The SCAD group consisted of 75.5% women compared to 31.9% of the non-SCAD MI group. The prevalence of cardiovascular risk factors, use of acetylsalicylic

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acid (ASA), statins and anti-hypertensive medications on admission was lower in the SCAD group. (Table 1)

Table 1. Baseline characteristics in SCAD and non-SCAD myocardial infarction (MI)

	SCAD MI n=147 n (%)	Non-SCAD MI n=32601 n (%)	p-value
Age	52.9 ±12.2	68.5 ±11.8	<0.01
Female gender	111 (75.5)	10391 (31.9)	<0.01
Diabetes	3 (2.0)	6921 (21.4)	<0.01
Hypertension[1]	39 (26.5)	19070 (59.4)	<0.01
Hyperlipidemia[2]	20 (13.7)	9125 (30.4)	<0.01
Smoking history[3]	56 (38.1)	17599 (58.1)	<0.01
Previous MI	16 (10.9)	6733 (21.1)	<0.01
Previous CABG	0	1996 (6.1)	<0.01
Previous PCI	6 (4.1)	5482 (16.8)	<0.01
ACE-I or ARBs	26 (17.7)	11904 (36.5)	<0.01
Beta-blockers	25 (17.1)	10107 (33.7)	<0.01
ASA	27 (18.5)	8577 (28.6)	<0.01
$P2Y_{12}$-inhibitor	4 (2.7)	1642 (5.5)	0.15
DAPT	3 (2.1)	951 (3.2)	0.44
OAC	7 (4.8)	2426 (7.6)	0.21
Statins	20 (13.7)	9125 (30.4)	<0.01

ACE-I = Angiotensin Converting Enzyme Inhibitor, ARB= Angiotensin Receptor Blocker, ASA = Acetyl Salicylic Acid, CABG= Coronary Artery Bypass Graft Surgery, DAPT= Dual Antiplatelet Therapy, MI= Myocardial Infarction, OAC= Oral Anticoagulants, PCI= Percutaneous Coronary Intervention, SCAD= Spontaneous Coronary Artery Dissection. [1]Anti-hypertensive treatment on admission. [2]Treatment with lipid lowering agents on admission. [3]Active or previous smoking history.

Procedural characteristics

SCAD patients more often presented with STEMI when compared to non-SCAD MI patients, 47.6% and 39.3%, respectively (p<0.01). Coronary artery occlusion was found in 17.7% of

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SCAD patients and 23.8% of non-SCAD MI patients, p=0.08. (Table 2) Coronary artery atherosclerosis was reported in 17 (11.6%) SCAD patients.

Type 1 dissection was found in 12.2%, type 2A/2B dissection in 72.8%, type 3 dissection in 4,1% and type 4 in 10.9% of SCAD patients (Figure 1). Intracoronary imaging, OCT/IVUS, was used in 24.5% of SCAD patients and in 3.9% of non-SCAD MI patients.

PCI was attempted in 40.1% of SCAD patients and 30.6% received stent. In non-SCAD MI patients corresponding figures were 70.9% and 65.8%, respectively.

In SCAD patients with 100% coronary artery occlusion underwent PCI of which 65.5% were treated with stent implantation. Patients with non-occlusive SCAD were treated with stent implantation in 23% of cases. Intracoronary imaging was used in 24.5 % of SCAD-procedures compared with 3.3% in non-SCAD MI. The general success of PCI was 86.4% in the SCAD group compared to 94.8% in the non-SCAD MI population, p<0.01. (Table 2)

Table 2. Coronary angiography, invasive and medical management in SCAD and non-SCAD myocardial infarction (MI)

	SCAD n=147 n (%)	Non-SCAD MI n=32601 n (%)	p-value
Coronary angiography, findings and procedures			
STEMI	70 (47.6)	12823 (39.3)	<0.01
Coronary artery occlusion	26 (17.7)	7601 (23.8)	0.08
Conservative management	88 (59.9)	9493 (29.1)	<0.01
Attempted PCI	59 (40.1)	23108 (70.9)	<0.01
PCI with stent	45 (30.6)	21455 (65.8)	<0.01
OCT/IVUS	36 (24.5)	1260 (3.9)	<0.01
General success*	51 (86.4)	21913 (94.8)	<0.01
Medical therapy at discharge			
ACE-I or ARBs	87 (59.2)	24187 (74.2)	<0.01
Beta-blockers	118 (81.9)	25370 (86.0)	0.16
ASA	134 (93.1)	26522 (89.9)	0.21
ASA only	17 (11.6)	3096 (9.5)	0.39
$P2Y_{12}$-inhibitor	123 (85.4)	24871 (84.3)	0.72
DAPT	117 (81.3)	23418 (79.4)	0.59
OAC	13 (8.8)	3935 (12.2)	0.22
Statins	110 (76.4)	27036 (91.7)	<0.01

ACE-I= Angiotensin Converting Enzyme Inhibitor, ASA= Acetylsalicylic Acid, ARB= Angiotensin Receptor Blocker, DAPT= Dual Antiplatelet Therapy, MI= Myocardial Infarction, OAC= Oral Anticoagulant, OCT/IVUS= Optical Coherence Tomography/Intravascular Ultrasound, PCI= Percutaneous Coronary Intervention, SCAD= Spontaneous Coronary Artery Dissection, STEMI= ST-segment Elevation Myocardial Infarction, *Subjective assessment by the operator. The operator has reached the main aim of the treatment.

Management stratified by type of dissection is presented in Supplementary Table 2.

Inpatient care time and medical treatment at discharge

There was no difference in days of hospitalisation during index event between the two groups, with a median of 4 days, p=0.93.

The use of betablockers, ASA, $P2Y_{12}$-inhibitors, DAPT and oral anticoagulants (OACs) was similar between the groups at discharge. SCAD patients received DAPT in 81.3% while 11.6% received ASA only and 2.7% received no antiplatelet therapy. Non-SCAD MI patients received more often ACE-I/ARBs and statins at discharge, yet statins were prescribed in 76.4% of SCAD cases. (Table 2, Figure 2)

Outcomes

Median follow up time for MACE was 17.3 months. There was no difference in rate of combined outcomes between the SCAD and the non-SCAD MI groups (10.9 and 13.4%, p=0.75). (Table 3, Figure 3)

Table 3. Outcome in SCAD and non-SCAD myocardial infarction

	SCAD MI n=147 n (%)	Non-SCAD MI n=32601 n (%)	p-value
Death	4 (2.7)	3099 (9.7)	<0.01
MI	3 (2.0)	1424 (4.4)	0.20
Acute coronary re-angiography	14 (9.5)	1495 (4.6)	<0.01

Version: 2021-11-14

after discharge			
MI= Myocardial Infarction, SCAD= Spontaneous Coronary Artery Dissection,			

Outcomes in SCAD subtypes are presented in Supplementary Table 3.

Median number of days to outcomes was 10 for SCAD and 25 for non-SCAD MI. The rate of all-cause mortality in SCAD (2.7%) was lower when compared to the non-SCAD MI population (9.7%) ($p<0.01$). There was no difference in the rate of re-infarction between the SCAD (2.0%) and the non-SCAD MI population (4.4%) ($p=0.20$). Median number of days until re-infarction in SCAD patients was 37 days. Median time to acute re-angiography was 12 (IQR: 127.5) days in the SCAD group and 14 (IQR: 208) days in the non-SCAD group which was statistically non-significant. The SCAD population was more often subject to acute re-angiography after the index event (9.5%) than the non-SCAD MI population (4.6%) ($p<0.01$). (Table 3)

Discussion

In this study with 100% nationwide coverage of MI patients undergoing coronary angiography during a two year period we found an incidence of SCAD at 0.74 cases per 100.000 inhabitants per year and a SCAD prevalence of 0.43% of all MI cases in Sweden at the time. The prevalence of SCAD in the MI population <50 years was 2.2% and 7.3% of MI cases in women <50 years. We found an equally high rate of combined outcomes and recurrent MI in the two MI groups whereas SCAD patients were more often subject to acute coronary re-angiography. Although 59.9% were treated conservatively without PCI or CABG, 81.3% of SCAD patients were discharged with DAPT.

Version: 2021-11-14

Epidemiology

While the prevalence of SCAD was lower than most other studies have suggested, we found a higher prevalence of SCAD than previously published multicenter studies. (20-22) An older study of 32 869 patients from 3 centers in western Denmark identified a SCAD prevalence of 0.2% during 8 years whereas a Japanese study of 20 195 MI patients collected in 20 centers during 13 years identified a SCAD prevalence of 0.31%. (20-22) Our results are in concordance with the recently published meta-analysis by Franke et al (23) including more than 2000 patients. In addition, we did not exclude patients with angiographic signs of atherosclerosis in other than SCAD vessels. On the other hand, when comparing with smaller single center studies, the prevalence in our cohort is lower. This might be attributed to the relatively new SCAD variable in SCAAR with an increasing learning curve among interventionists to recognise and report all types of SCAD in the SCAAR registry. Thus, a certain underdiagnosis may have caused a lower degree of identification of SCAD cases than in centers with special interest in SCAD.

We also found a lower prevalence of SCAD in female MI patients <50 years (7.3%) compared to previous studies. Four studies have reported a SCAD prevalence of 23-36% in women below 50-60 years with MI. Three of these are small single center studies including ≤ 20 SCAD cases less than 60 years. (1, 20, 21) The fourth by Nakashima et. al. reported a SCAD prevalence of 35% in women <50 years with MI. (11) This is in contrast to our findings and we speculate it to be related to genetic variations and a low prevalence of CAD in Japan.

Version: 2021-11-14

Risk factors

Our results are in line with previous studies showing that SCAD predominantly affects middle-aged women with a low prevalence of cardiovascular risk factors and ongoing cardiovascular medications.(1, 2, 4, 9, 11, 12, 14, 18, 20) Interestingly, 10% of SCAD cases included in our study had suffered a previous MI. This may be explained by SCAD recurrency as we do not know if the indexed SCAD occasion was the first. Rate of recurrency has been described to be between 4.7-17% in 2-4 years which aligns with our findings. (11, 12, 14) Other possible explanations are inclusion of patients with concurrent atherosclerosis in other coronary segments than the one affected by SCAD.

Sex

Our SCAD population included 25% men which is in contrast to previous studies - in particular to those where SCAD patients with atherosclerosis have been excluded.(1, 9, 11) However, there are studies with a proportion of male patients between 23% and 46.2%.(21, 22) A consequence of excluding all SCAD patients with any atherosclerosis is the selection of younger and female patients, with a low burden of concomitant co-morbidity. When describing findings from imaging, genetic or proteomic studies there could be a rationale to select patients with a clear-cut SCAD diagnosis. On the other hand, when describing incidence, prevalence, management and prognosis, it is of great importance not to introduce a selection bias by excluding patients with concomitant atherosclerotic manifestations. The current study included all patients with SCAD unless iatrogenic or due to plaque rupture and hence describes the entire SCAD population without selection. Our results indicate that also men are, to a larger extent than previously thought, affected by SCAD, and that the diagnosis should not be overlooked but sought after in these patients too.

Version: 2021-11-14

Angiography and intervention

Type 2 dissection was the most common angiographic manifestation, in accordance with previous studies, followed by type 1, however only seen in 12.2% as opposed to 29-55% in previous reports. Meanwhile, the prevalence of type 3 was similar between this and other studies.(1, 4, 9, 11) This indicates that intimal flap appearance and dual lumen sign is less prevalent than previously suggested, probably due to increasing recognition of non-classical appearance of SCAD. Although intravascular imaging was more widely used in SCAD patients, a majority of type 3 and 4 SCAD cases were diagnosed without using OCT/IVUS. As type 3 is defined as angiographically indistinguishable from atherosclerotic coronary artery disease, diagnosing type 3 without intravascular imaging is a limitation in this study.

There are several feasible reasons for this, including technical difficulties in the case of distal occlusions or ignorance of its necessity. In addition, the diagnosis of SCAD mimicking CAD does not always require intravascular imaging but can be made with enough experience without arduous catheterisation.

SCAD patients underwent PCI and stenting less frequently at the index event than non-SCAD MI patients, although PCI was attempted in 40% of cases and 30% received stents. Other retrospective studies of SCAD patients have reported revascularisation rates between 12-56%.(4, 5, 9, 11, 24) As there are no RCTs describing optimal management, we cannot comment on over- or undertreatment. Nor do we have information regarding the clinical circumstances underlying choice of treatment e.g., PCI on vital indication in hemodynamically unstable patients.

Version: 2021-11-14

Medication

We found the medication at discharge to be remarkably similar in patients with SCAD and non-SCAD MI, including the use of ASA, $P2Y_{12}$-inhibitors and DAPT. This might reflect adherence to current guidelines for ACS in the absence of SCAD specific evidence. (6, 7) In the current study 80% of SCAD patients were treated with betablockers, which has been proposed to be beneficial.(15) In a retrospective study of 327 patients the use of betablockers was associated with a lower risk of recurrent SCAD and this therapy could therefore be considered. (6, 7) The prescription rate of statins was high in SCAD patients, despite not being recommended. (6, 7). Our findings thus reflect the lack of familiarity that most cardiologists may have had with managing SCAD, especially prior to 2018, which is the period when our patients were included.

Outcomes

The overall rate of outcomes did not differ between SCAD and non-SCAD MI. However, all-cause mortality was lower in SCAD, yet the rate of recurrent MI was equal. Furthermore, SCAD patients were more often subject to acute coronary re-angiography after the index event, 9.5%. This is evidence of significant morbidity in SCAD, especially as age and cardiovascular risk factors have not been adjusted for, due to the relatively small study population with SCAD. In 3 recently published European SCAD-studies (16-18) the unplanned re-angiography was 4%, 8.5% and 5.3% respectively. The present study found a death rate of 2.7% after a median follow-up of 17.3 months indicating a higher mortality than in previous studies. This could be caused by inclusion of a more representative and unselected population of SCAD patients.

Although recurrent MI was equal between the two groups, our 2% recurrency rate is lower than previously described, varying between 4.8-12% per year.(11, 15) SCAD recurrency has been reported at 4.7-17% in 22-47 months. (11, 12, 14) The discrepancy between our study and the American and Canadian series is however small and may be due to different lengths of follow-up as adverse events may not be evenly distributed in time. (12, 15)

The cause of the high rate of acute, unplanned coronary re-angiography after the index event is not known to us and is not explained by recurrent MI or need for revascularization as PCI was attempted in only 5/14 acute coronary re-angiographies. Further studies are needed to elucidate this, although it is plausible that a high prevalence of recurrent angina and difficulties in chest pain risk assessment could be contributing factors.

Strengths and limitations

This study has identified all patients in Sweden considered having SCAD during the study period, and all centers performing invasive coronary angiography are represented. All angiographies where SCAD has been reported in the SCAAR registry have been reviewed and validated by an independent interventional cardiologist. All data regarding demographics, management, treatment and in-hospital outcomes are immediately registered on-line, thus limiting recall bias and missing values as these variables are compulsory to register. Limitations of this study include possible heterogeneity in the confirmation of SCAD diagnosis as the study did not include a core-lab. Segment distribution in SCAAR in angiography alone is not compulsory, therefore it is missing information in many SCAD patients. A segment analysis was not done. The occurrence of FMD was not available. Additionally, data that could not be derived from angiographic re-evaluation was derived from registries. Predictors of MACE were not analysed in this small population.

Conclusion

Version: 2021-11-14

SCAD patients were comparatively young and previously healthy, yet suffered substantial mortality and morbidity and are frequently subject to acute coronary re-angiography and its accompanying risks. As both incidence and prevalence are low, data highlight the careful need of diagnostic awareness in both men and women and in patients with co-existing atherosclerotic coronary artery disease.

Author statement

H Wilander, S Sederholm Lawesson, D Venetsanos and E Swahn are responsible for the conception and design of the study, have full access to all data, analysed and interpreted the data and drafted the manuscript. C Pagonis gathered the PCI data, critically revised the manuscript and added important intellectual content. C Dworeck, L Jonasson, N Johnston, T Kellerth, P Tornvall and T Yndigegn critically revised the manuscript and added important intellectual content.

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Impact on daily practice

As knowledge is very scarce regarding SCAD-patients, a nationwide study on all-comers like this, reflects the lack of familiarity that most cardiologists may have had with managing SCAD, especially prior to 2018. Based on the findings of this observational study, a continued effort to increase the knowledge, awareness and reporting of SCAD in our national quality registry (SCAAR) through randomised registry clinical trials (RRCT) is ongoing. The authors believe that this will change current practice in Sweden in the coming years.

Version: 2021-11-14

Disclosure

The Authors declare that there are no conflicts of interest.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Version: 2021-11-14

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Version: 2021-11-14

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Version: 2021-11-14

Figure legends

Figure 1. **Distribution of SCAD subtypes.**

Figure 2. **Medical therapy at discharge.**

Figure 3. **Outcomes in SCAD and non-SCAD MI.**

Figure 1.

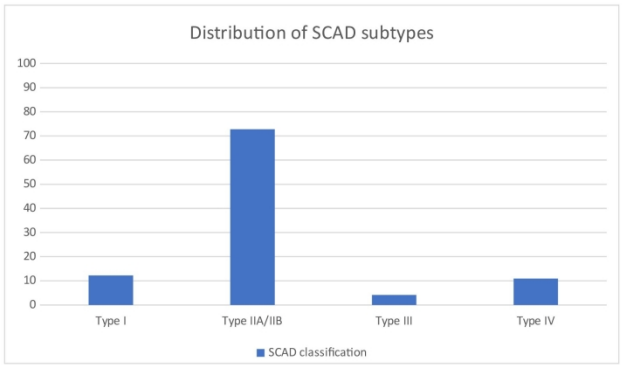

Figure 1

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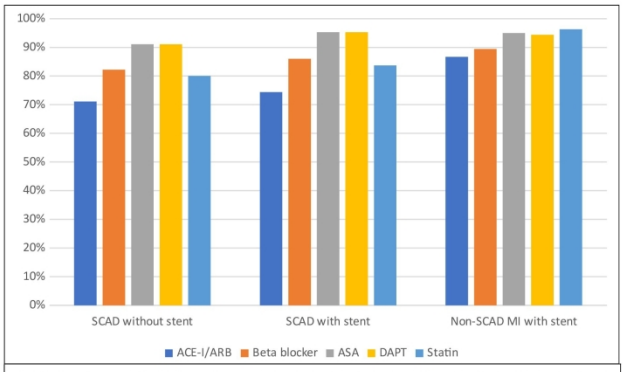
Figure 2.



SCAD = Spontaneous Coronary Artery Dissection, MI = Myocardial Infarction, ACE-I = Angiotensin Converting Enzyme Inhibitor, ARB = Angiotensin Receptor Blocker, ASA = Acetylsalicylic Acid, DAPT = Dual Antiplatelet Therapy.

Figure 2

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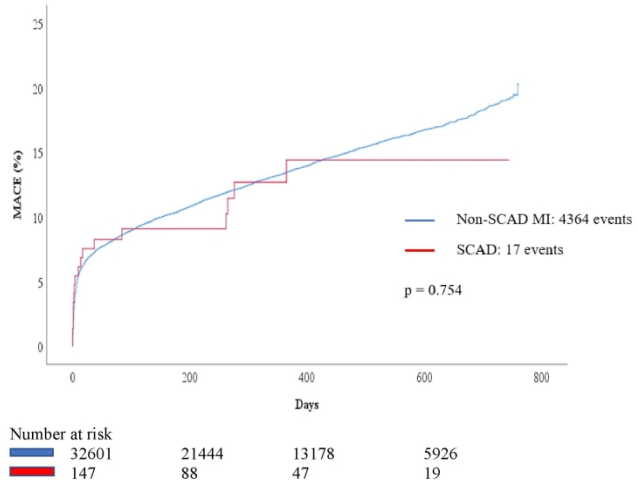
Figure 3.



MACE = Major Adverse Cardiac Events, SCAD = Spontaneous Coronary Artery Dissection, MI = Myocardial Infarction.

Figure 3

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SweSCAD: Supplementary tables and figures

Supplementary Table 1. Saw angiographic classification of SCAD

	Classification
SCAD type 1	The classical angiographic radiolucent 'flap' and linear double lumen.
SCAD type 2a/2b	A long diffuse and smooth stenosis predominantly located in mid-to-distal segments, and classical signs of a dissection as in Type 1 are missing; Type 2a: Distal vessel normal; Type 2b: The stenosis extends angiographically to the end of the vessel.
SCAD type 3	Angiographically indistinguishable from a focal atherosclerotic stenosis requiring diagnostic confirmation by OCT or IVUS.
SCAD type 4	Total occlusion. The diagnosis established once coronary flow is re-established or inferred by subsequent vessel healing and the exclusion of an embolic cause.

Supplementary Table 2. Coronary angiography and invasive management in SCAD subtypes

	Saw Classification (index event)	I n=18 (%)	IIA/IIB n=107 (%)	III n=6 (%)	IV n=16 (%)
Diagnostic features	STEMI	7 (38.9)	47 (43.9)	5 (83.3)	11 (68.8)
	OCT/IVUS used	4 (22.2)	26 (24.3)	2 (33.3)	4 (25.0)
Invasive management	Conservative management	13 (72.2)	67 (62.6)	5 (83.3)	3 (18.8)
	Attempted PCI	5 (27.8)	40 (37.4)	1 (16.7)	13 (81.3)
	PCI with stent	5 (27.8)	31 (29.0)	1 (16.7)	8 (50.0)
	General success*	4 (80)	35 (87.5)	1 (100%)	11 (84.6)

MI= Myocardial Infarction, OCT/IVUS= Optical Coherence Tomography / IntraVascular UltraSound, PCI= Percutaneous Coronary Intervention, SCAD= Spontaneous Coronary Artery Dissection, STEMI= ST-segment Elevation Myocardial Infarction.
*Subjective assessment by the operator. The operator has reached the main aim of the treatment.

Supplementary Table 3. Outcome in SCAD subtypes

	I n=18 (%)	IIA/IIB n=107 (%)	III n=6 (%)	IV n=16 (%)
Death	2 (11.1)	0 (0)	0 (0)	2 (12.5)
MI	0 (0)	3 (2.8)	0 (0)	0 (0)
Acute coronary re-angiography	1 (5.5)	10 (9.3)	1 (16.7)	2 (12.5)
MI = Myocardial Infarction, SCAD = Spontaneous Coronary Artery Dissection,				

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	14
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9 NA NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.