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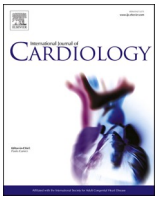

Twenty-five-year trends in incidence, angiographic appearance, and management of spontaneous coronary artery dissection☆

Michael Würdinger [a], Victor Schweiger [a], Thomas Gilhofer [a], Victoria L. Cammann [a], Annika Badorff [a], Iva Koleva [a], Davide Di Vece [a], David Niederseer [a], Alessandro Candreva [a], Jonathan Michel [a], Alexander Gotschy [a], Julia Stehli [a], Barbara E. Stähli [a], Jelena R. Ghadri [a], Christian Templin [a,*]

[a] University Heart Center, Department of Cardiology, University Hospital Zurich, and University of Zurich, Zurich, Switzerland

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ABSTRACT

Background: Spontaneous coronary artery dissection (SCAD) has been described as an infrequent cause of acute coronary syndrome (ACS). Knowledge about the disease is still limited and SCAD might still be underdiagnosed.
Objectives: Trends in incidence, presentation, angiographic appearance, management, and outcomes of SCAD over 25 years were analyzed.
Methods: Patients with SCAD between 1997 and 2021 at the University Hospital Zurich, Switzerland, were included. Incidences were assessed as total numbers and proportions of ACS cases. Clinical data were collected from medical records and angiographic findings were reviewed. Major adverse cardiac events (MACE) were defined as the composite of all-cause death, cardiac arrest, SCAD recurrence or progression, other myocardial infarction, and stroke.
Results: One hundred fifty-six SCAD cases were included in this study. The incidence increased significantly in total ($p < 0.001$) and relative to ACS cases ($p < 0.001$). This was based on an increase of shorter lesions ($p = 0.004$), SCAD type 2 ($p < 0.001$), and lesions in side branches ($p = 0.014$), whereas lesions in the left main coronary artery and proximal segments were decreasing (p-values 0.029 and < 0.001, respectively). There was an increase in conservative therapy ($p < 0.001$). The rate of MACE (24%) was stable, however, there was a reduced proportion of patients with a need for intensive care treatment ($p = 0.017$).
Conclusions: SCAD represents an important entity of ACS that still might be underappreciated. The increasing incidence of SCAD is likely based on better awareness and familiarity with the disease. A lower need for intensive care treatment suggests positive effects of the increasing implementation of conservative management.

1. Introduction

Spontaneous coronary artery dissection (SCAD) has been reported as an infrequent cause of myocardial ischemia that predominantly affects younger women. Since its first description in 1931 [1], SCAD has been considered to be rare and commonly related to pregnancy [2]. However, SCAD has been increasingly recognized as an important entity of acute coronary syndrome (ACS). It has been shown to be responsible for up to 4% of all ACS and up to 45% of ACS cases in female patients under 50 years of age [3]. SCAD is frequently associated with emotional or physical triggers and predisposing conditions such as fibromuscular dysplasia (FMD), among others [4–8]. However, the exact pathophysiologic mechanisms are yet to be elucidated.

SCAD results from a spontaneous tear in the coronary artery wall

Abbreviations: ACS, Acute coronary syndrome; CABG, Coronary artery bypass-graft; FMD, Fibromuscular dysplasia; LAD, Anterior descending artery; LCX, Left circumflex artery; LMCA, Left main coronary artery; MACE, Major adverse cardiac events; NSTEMI, Non-ST-elevation myocardial infarction; PCI, Percutaneous coronary intervention; RCA, Right coronary artery; SCAD, Spontaneous coronary artery dissection; STEMI, ST-elevation myocardial infarction; UAP, Unstable angina pectoris.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

* Corresponding author at: Director Andreas-Grüntzig-Heart-Catheter-Laboratories, Cardiology, University Heart Center, University Hospital Zurich & University of Zurich, Rämistrasse 100, 8091 Zürich, Switzerland.
E-mail address: christian.templin@usz.ch (C. Templin).

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with consequent myocardial ischemia. There are two pathophysiological mechanisms leading to SCAD. The first is an intimal flap with formation of a false lumen. The second is the formation of an intramural hematoma without an intimal lesion, presumably by hemorrhage of the vasa vasorum [9]. These mechanisms also have prognostic implications with worse outcomes in patients with intramural hematoma at baseline [10–12]. SCAD is classified into different types by means of its angiographic appearance [13,14]. Invasive coronary angiography is recommended for diagnosis of SCAD based on its high spatial and temporal resolution compared to noninvasive imaging [13]. Recommendations for the management of SCAD are currently based on observational studies and expert opinion. Conservative treatment is recommended for stable patients due to high rates of spontaneous healing [15], whereas interventional treatment is reserved for high-risk situations such as ongoing ischemia, hemodynamic instability, or high-risk anatomy [16].

Scientific interest in SCAD has increased clearly within the last decades and most articles have been published within the last ten years [3]. Concomitantly, there is a rising awareness among physicians and a better understanding of epidemiology, pathophysiological mechanisms, and risk factors. For this reason, it was our intent to analyze trends in incidence, presentation, angiographic appearance, management, and outcomes of SCAD over the 25 years.

2. Methods

2.1. Study population

Patients with clinical and angiographic diagnosis of SCAD from January 1997 to December 2021 at the University Hospital Zurich, Switzerland, were eligible for inclusion in the study. Patients were diagnosed with SCAD during clinical routine by the interventional cardiologists. Patients were included prospectively since 2020. Retrospectively included SCAD patients were identified by data query of electronical medical records for "spontaneous coronary artery dissection". Only patients with given informed consent were included in the study. Both elective and emergency coronary angiographies were assessed. All angiograms of identified patients were reviewed by two independent physicians to confirm the diagnosis of SCAD. In uncertain cases a consensus was reached within experienced interventional cardiologists of the team. Angiographic criteria described by Saw et al. 2014 [13] were applied for the diagnosis of SCAD in all patients during the reevaluation of coronary angiograms. SCAD lesions were divided into four types depending on the angiographic appearance: type 1 is characterized by an intimal flap and contrast dye staining of multiple lumens. The other angiographic types are characterized by the presence of an intramural hematoma: type 2 is characterized by a long diffuse and smooth stenosis. Type 3 is defined as a focal or tubular stenosis as described before [13]. A fourth type has been proposed later and is defined as an abrupt vessel occlusion [14]. Multivessel SCAD was defined as separate lesions in different coronary territories that appeared simultaneously. Patients with iatrogenic dissections were excluded from the study. The observed incidence of SCAD was calculated both as a total number and as a proportion of all ACS cases. The numbers of total ACS patients were taken from the ACS database of the University Heart Center, Zurich.

2.2. Management and follow-up

Patients with SCAD were managed according to the judgement of the treating physicians. Hospital records were analyzed, and patient history, presentation, diagnostic parameters, treatment, and major adverse cardiac events (MACE) were recorded. Myocardial infarction was defined as proposed in the fourth universal definition of myocardial infarction [17] for all patients. MACE were defined as the composite of all-cause death, cardiac arrest, SCAD recurrence or progression, myocardial infarction due to any other cause, and stroke. SCAD progression was defined as an angiographic progression of the first lesion before healing, whereas SCAD recurrence was defined as a new lesion distinct from the first or within the same segment after complete healing. Patient history and follow-up data were collected from medical records and, in case of no further clinical follow-up, phone interviews of the patients.

2.3. Statistical analysis

Statistical analyses and compilation of graphs were performed using SPSS version 29.0 (IBM) and R 4.1 (R Foundation). Continuous variables were provided as means and standard deviations or medians and interquartile ranges, and categorical variables as numbers with percentages. A p-value of <0.05 was considered statistically significant. P-values for trends were calculated by the Mann-Kendall trend test (Kendall's tau) for continuous variables and by the Mantel-Haenszel test for trends (Linear-by-linear association) for categorical variables. Continuous variables were compared by the Student's t-test or Mann–Whitney U test and categorical variables by the Pearson χ^2 test or Fisher's exact test.

2.4. Ethics approval

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and has been approved by the Cantonal Ethics Committee Zurich, Switzerland.

3. Results

3.1. Patient characteristics and incidence

One hundred fifty-six cases of SCAD were included in the study. Out of these, 146 patients had first SCAD events, and ten patients had SCAD recurrences. One hundred sixteen cases of SCAD occurred in female patients (74%). The median age was 52 years (IQR, 42–60 years). Men were more likely to present with unstable angina pectoris (UAP) than women (20.0% vs. 5.2%, $p = 0.005$), whereas the incidence of ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) did not differ between sex groups (p-values 0.082 and 0.901, respectively). There was no trend in sex distribution and median age (p-values 0.381 and 0.369, respectively).

The incidence of SCAD increased significantly over the study period, from six patients within the first five years to 79 patients within the last five years ($\tau = 1.000$, $p < 0.001$). This increase was also significant, when calculated as a proportion of all ACS cases ($p \leq 0.001$). SCAD was the underlying cause of ACS in 1.6%, with a rate of 2.2% in the last five years of the study period. (Table 1, Fig. 1).

3.2. Presentation, associated conditions, and trigger factors

All patients presented with an ACS. Seventy-seven patients (49%) presented with STEMI, 65 patients (42%) with NSTEMI, and 14 patients (9%) with UAP. There was no significant change in ACS types over the study period ($p = 0.859$) (Table 1). The majority of patients (77%) was diagnosed within 24 h after symptom onset, and only a minority (17%) presented after 48 h or later. There were no trends in the time point of presentation in this study (p-values 0.129 and 0.69, respectively). Twelve patients (8%) presented with cardiac arrest, however, in this context, no trend could be observed over the study period ($p = 0.966$). Killip classification was used for all ACS types to categorize the severity of ACS. One hundred twenty-nine patients (83%) were categorized to Killip class 1, five patients (3%) to Killip class 2, three patients (2%) to Killip class 3, and 18 patients (12%) to Killip class 4. The severity of ACS according to Killip classification did not change ($p = 0.996$) (Table 1). Median LVEF, proportions of patients with normal, mildly reduced and severely reduced LVEF, and LVEDP at presentation did not have any trend over the years (p-values 0.538, 0.566, 0.724, 0.258, and 0.992,

Table 1
SCAD Incidence, Patient Characteristics and Presentation [N (%)].

	1997–2001		2002–2006		2007–2011		2012–2016		2017–2021		Total		P-value[a]
Incidence [N (N SCAD/N ACS, % of ACS[b])]	6	(na)	7	(na)	23	(23/2335, 1.0)	41	(41/3521, 1.2)	79	(79/3678, 2.2)	156	(156/ 9534, 1.6)	**<0.001 (<0.001)**
Sex													
Male	3	(50)	4	(57)	3	(13)	9	(22)	21	(27)	40	(26)	0.381
Female	3	(50)	3	(43)	20	(87)	32	(78)	58	(73)	116	(74)	0.381
Age [Median (IQR)]	41	(28, 55)	52	(40, 58)	54	(44, 66)	48	(41, 57)	53	(43, 61)	52	(42, 60)	0.369
ACS Type													
STEMI	3	(50)	3	(42)	14	(61)	18	(44)	39	(49)	77	(49)	0.784
NSTEMI	1	(17)	2	(29)	9	(39)	20	(49)	33	(42)	65	(42)	0.292
UAP	2	(33)	2	(29)	0	(0)	3	(7)	7	(9)	14	(9)	0.181
Killip Classification													
1	5	(83)	7	(100)	18	(78)	33	(83)	66	(84)	129	(83)	0.847
2	0	(0)	0	(0)	1	(4)	1	(2)	3	(4)	5	(3)	0.607
3	0	(0)	0	(0)	0	(0)	2	(5)	1	(1)	3	(2)	0.773
4	1	(17)	0	(0)	4	(18)	4	(10)	9	(11)	18	(12)	0.855
Out-of-Hospital Cardiac Arrest	0	(0)	0	(0)	3	(13)	4	(10)	5	(6)	12	(8)	0.966
LVEDP [Median (IQR)]	6	(6)	18	(12, 20)	18	(13, 22)	17	(13, 23)	17	(13, 21)	17	(13, 22)	0.992
LVEF													
≥ 50%	3	(50)	6	(86)	15	(68)	29	(78)	27	(73)	110	(73)	0.566
41–49%	1	(17)	0	(0)	3	(14)	6	(16)	11	(14)	21	(14)	0.724
≤ 40%	2	(33)	1	(14)	4	(18)	2	(5)	10	(13)	19	(13)	0.258
Lab Values													
CK Peak Levels [Times ULN, median (IQR)]	NA		1.7	(1.0, 12.1)	2.8	(1.2, 7.5)	4.3	(2.5, 9.6)	3.2	(1.0, 6.1)	3.4	(1.5, 7.1)	0.900
Troponin Peak Levels [Times ULN, median (IQR)]	NA		5.0	(1.5, 45.9)	17.5	(9.1, 90.4)	91.9	(40.5, 228.8)	61.8	(18.8, 117.7)	63.0	(16.3, 140.1)	0.092
BNP Peak Levels [Times ULN, median (IQR)]	NA		8.6	(2.5, 23.3)	6.1	(2.3, 11.6)	4.3	(1.1, 8.7)	3.2	(1.6, 9.0)	3.6	(1.6, 9.3)	0.132

Abbreviations: BNP, brain natriuretic peptide; CK, creatine kinase; IQR, interquartile range; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction; NA, not applicable; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.; ULN, upper limit of normal.

[a] *P*-values calculated using Mann-Kendall trend test for absolute numbers and Mantel-Haenszel test for proportions of the total numbers.

[b] beginning from 2007.

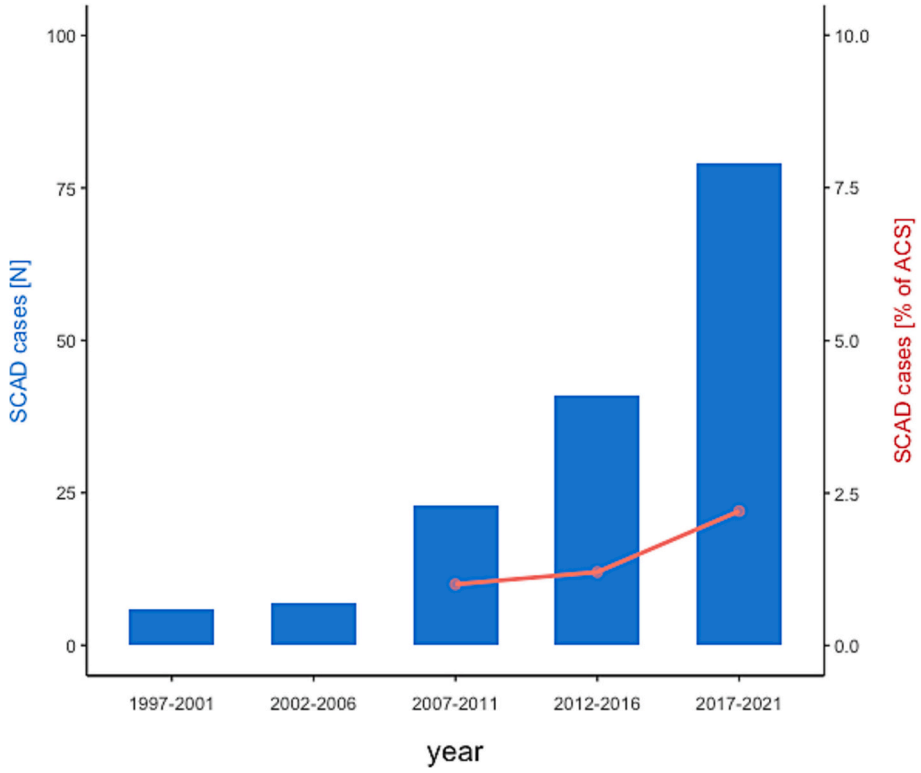

Fig. 1. Incidence of SCAD as total numbers and percentage of all ACS. Both absolute numbers of SCAD patients and percentages of SCAD in all ACS cases increased significantly over the study period (*p*-values <0.001 and < 0.001, respectively).

respectively). Peak values of creatine kinase (CK), cardiac troponin, and brain natriuretic peptide (BNP) did also not change during the study period (p-values 0.900, 0.092, and 0.132, respectively) (Table 1).

Associated conditions and trigger factors are shown in Table 2. Overall, associated conditions for SCAD were identified in 97 patients (62%). Of these, 46 patients (47.4%) had more than one identified associated condition with SCAD. The proportion of patients with established associated conditions and the number of those did not change over the study period (*p*-values 0.165 and 0.636, respectively). Arteriopathies were present in 25 cases (16%), most of these (20, 13%) were due to FMD. One patient had Marfan syndrome, one patient Ehlers-Danlos syndrome, and the remaining undifferentiated arterial lesions such as dissections and non-atherosclerotic stenoses of arteries. No significant trend could be found both in the detection of FMD and of other arteriopathies. Screening for FMD was performed in 65% of patients, either by computed tomography angiography (40%), magnetic resonance angiography (19%), digital subtraction angiography (19%), or duplex sonography (21%) of at least the renal arteries, with better screening rates in the later years of the study period (75% during the last five years, $p = 0.003$). Complete head-to-pelvis arterial screening was performed in 38% of patients with a clear trend to better screening rates in the later years of the study period (57% during the last 5 years, $p < 0.001$). A trend could be observed in an increasing proportion of patients with migraine and other neurologic disorders ($p = 0.046$). The shares of patients with other associated conditions were constant. An acute trigger was found in 78 of all SCAD cases (50%). A physical trigger was identified in 50 patients (32%), and an emotional trigger was found in 42 patients (27%). 14 patients (9%) had both an emotional and physical trigger. The proportion of patients with an acute trigger did not change ($p = 0.656$).

3.3. Angiographic characteristics

Overall, 34 patients (23%) presented with SCAD type 1, 106 patients (68%) with SCAD type 2, eight patients (5%) with SCAD type 3 and eight patients with SCAD type 4 (5%) (Table 3). There was a significant trend towards a lower proportion of SCAD type 1 ($p < 0.001$) and a higher proportion of SCAD type 2 ($p < 0.001$) over the study period (Fig. 2A). SCAD was found in the left main coronary artery (LMCA) in eight patients (6%), in the left anterior descending artery (LAD) in 62 patients (44%), in the left circumflex artery (LCX) in 53 patients (38%), and in the right coronary artery (RCA) in 17 patients (12%). Sixteen patients (10%) presented with a multivessel SCAD (Table 3). There was a decreasing trend of SCAD in the LMCA ($p = 0.017$; Fig. 2B). SCAD was detected more frequently in coronary side branches ($p = 0.014$), whereas the proportion of SCAD in proximal segments was decreasing ($p < 0.001$; Fig. 2C). The number of involved segments was decreasing from three to one segment over time ($p = 0.004$). Intracoronary imaging was used only in a minority of patients (17 cases, 11%) to confirm the diagnosis of SCAD, and there was no trend in the application of optical coherence tomography or intravascular ultrasound.

3.4. Management

Median hospital duration was 5 days (IQR, 3–10 days) and constant during the observation interval ($p = 0.848$). Twenty-seven patients (17%) needed intensive care treatment with a decreasing trend over the study period ($p = 0.017$). The proportion of patients, who needed mechanical support (i.e., extracorporeal life support, microaxial flow pump, or intraaortic balloon pump) or respiratory therapy (i.e., invasive, and non-invasive ventilation) was significantly decreasing (*p*-values 0.010 and 0.027, respectively), as well. The need of pharmacological vasoactive therapy did not change ($p = 0.074$) (Table 4).

Most cases were treated conservatively (100 patients, 64%). Percutaneous coronary intervention (PCI) was performed as the initial treatment in 52 patients (33%), coronary artery bypass graft (CABG) in six patients (4%). There were highly significant trends towards more conservatively treated patients and less patients with PCI or CABG treatment (*p*-values <0.001, 0.002, and 0.001, respectively) (Table 4). These trends were detectable both in patients with STEMI and NSTEMI (p-values 0.002 and 0.002, respectively). Trends in SCAD types and localization of lesions were the same in the PCI group as in the conservative treatment group. High-risk anatomical lesions, i.e. lesions of the left main coronary artery or proximal two-vessel disease, as defined in the current SCAD scientific statement of the ACC/AHA [18], were present in 42% of patients treated with PCI. This rate was significantly higher in the PCI group than in the conservatively treated group ($p < 0.001$). Choice of PCI technique did not change over time ($p = 0.879$); most patients were treated by stent implantation (41 patients, 79%). Only a minority of patients was treated by balloon angioplasty only, thrombus aspiration, or other interventions. Complications of PCI were noted in nine patients (17%) and did not demonstrate any trend over the study period ($p = 0.981$).

Medical therapy did not change over the last quarter of the century (Table 4). Most patients were treated with dual antiplatelet, dual antithrombotic, or triple antithrombotic therapy after discharge (132 patients, 85%). The median duration of DAPT was 12 months (IQR, 3–12 months) with 60% of patients receiving DAPT for this duration. No trend in the duration of DAPT was found during the study period ($p = 0.372$). Ninety-four patients (62%) received statins, 107 patients (71%) betablockers, 115 patients (76%) angiotensin converting enzyme inhibitors or angiotensin receptor blockers, five patients (3%) mineralocorticoid receptor antagonists, and 25 patients (17%) calcium channel blockers.

3.5. Outcomes

The median follow-up period was 727 days (IQR, 75–2021 days). Major adverse cardiovascular events (MACE) occurred in 38 cases (24%) with less than half of MACE occurring during hospitalization (16 cases,

Table 2
Associated Conditions and Acute Trigger Factors [N (%)].

	1997–2001		2002–2006		2007–2011		2012–2016		2017–2021		Total		P-value[a]
Associated Condition	2	(33)	3	(43)	17	(74)	22	(54)	53	(67)	97	(62)	0.165
Peripartum	1	(17)	0	(0)	3	(13)	3	(7)	2	(3)	9	(6)	0.086
Hormone Substitution	0	(0)	1	(14)	3	(13)	4	(10)	6	(8)	14	(9)	0.764
FMD and Other Arteriopathies	1	(17)	0	(0)	6	(26)	6	(15)	13	(17)	26	(17)	1.000
Systemic Inflammatory Disease	0	(0)	0	(0)	4	(17)	3	(7)	9	(11)	16	(10)	0.535
Migraine or Other Neurologic Disorder	0	(0)	1	(14)	8	(35)	10	(24)	30	(38)	49	(31)	**0.046**
Psychiatric Disorder	0	(0)	1	(14)	5	(22)	9	(22)	16	(20)	31	(20)	0.431
Illicit Drugs	0	(0)	0	(0)	0	(0)	0	(0)	6	(8)	6	(4)	0.050
Acute Trigger	3	(50)	3	(43)	12	(52)	18	(44)	42	(53)	78	(50)	0.656
Physical Stress	3	(50)	2	(29)	6	(26)	13	(32)	26	(33)	50	(32)	0.912
Emotional Stress	0	(0)	1	(14)	8	(35)	8	(20)	25	(32)	42	(27)	0.153

Abbreviations: FMD, fibromuscular dysplasia.
[a] *P*-values calculated using Mantel-Haenszel test for proportions of the total numbers.

Table 3
Angiographic Characteristics [N (%)].

	1997–2001		2002–2006		2007–2011		2012–2016		2017–2021		Total		P-value[a]
SCAD Type													
1	4	(67)	5	(71)	10	(44)	5	(12)	10	(13)	34	(22)	**<0.001**
2	2	(33)	1	(14)	11	(48)	33	(81)	59	(75)	106	(68)	**<0.001**
2 A	1	(17)	1	(14)	5	(22)	12	(29)	29	(37)	48	(31)	0.062
2B	1	(17)	0	(0)	6	(26)	21	(51)	30	(38)	58	(37)	0.064
3	0	(0)	0	(0)	0	(0)	2	(5)	6	(8)	8	(5)	0.108
4	0	(0)	1	(14)	2	(9)	1	(2)	4	(5)	8	(5)	0.679
SCAD Vessel													
Singlevessel	4	(67)	7	(100)	22	(96)	36	(88)	71	(90)	140	(90)	0.721
LMCA	0	(0)	1	(14)	4	(18)	2	(6)	1	(1)	8	(6)	**0.029**
LAD	3	(75)	1	(14)	9	(41)	17	(47)	32	(45)	62	(44)	0.847
LCX	0	(0)	3	(43)	7	(32)	13	(36)	30	(43)	53	(38)	0.326
RCA	1	(25)	2	(29)	2	(9)	4	(11)	8	(11)	17	(12)	0.250
Multivessel	2	(33)	0	(0)	1	(4)	5	(12)	8	(10)	16	(10)	0.721
Proximal Beginning of SCAD													
Proximal Segment	5	(83)	4	(57)	9	(39)	8	(20)	17	(22)	43	(28)	**<0.001**
Mid Segment	0	(0)	1	(14)	5	(22)	8	(20)	14	(18)	28	(18)	0.603
Distal Segment	1	(17)	2	(29)	2	(9)	9	(22)	17	(22)	31	(20)	0.548
Side Branch	0	(0)	0	(0)	7	(30)	16	(39)	31	(39)	54	(35)	**0.014**
Number of Segments [Median (IQR)]	3	(1, 6)	2	(1, 3)	2	(1, 3)	1	(1, 3)	1	(1, 2)	1	(1, 2)	**0.004**

Abbreviations: IQR, interquartile range; LAD, left anterior descending artery; LCX, left circumflex; LMCA, left main coronary artery; RCA, right coronary artery; SCAD, spontaneous coronary artery dissection.

[a] *P*-values calculated using Mann-Kendall trend test for absolute numbers and Mantel-Haenszel test for proportions of the total numbers.

10%). Of these, six patients (4%) developed cardiac arrest, and seven patients (5%) died during follow-up. Eight patients (5%) had a local progression of SCAD, and 11 patients (7%) had SCAD recurrence. Eight patients (5%) developed myocardial infarction that was not associated with SCAD recurrence or progression, e.g., due to stent thrombosis. One patient (1%) developed stroke after SCAD. No significant trends were found regarding total MACE and mentioned adverse outcomes during the study period. (Table 4). However, there was a trend to a lower number of patients with severely impaired LVEF ($\leq$ 40%) during follow up ($p = 0.012$) (Table 4).

4. Discussion

This study demonstrated long-term trends in incidence, diagnosis, angiographic appearance, management, and prognosis of SCAD. Major findings were a significant rise of SCAD incidence over the last quarter of a century and a change in therapy towards more conservative treatment strategies.

4.1. Incidence and angiographic appearance

The study illustrates a clearly growing trend of SCAD as an entity of ACS over the long-term. This finding is consistent with a study reporting population-based temporal incidences of SCAD in the United States until 2009 [19]. The increasing incidence of SCAD might be due to a higher awareness of clinicians and a better familiarity with its angiographic appearance rather than a true increase of the disease in the population. Rising scientific interest within the last ten years and the publication of an angiographic classification [13] as well as position papers from the European Society of Cardiology and the American Heart Association [18,20] might have contributed to this development. Two thirds of SCAD cases were classified as type 2 and most SCAD lesions were found in the LAD and LCX territory, consistent with previously published data [4,21,22]. There was a distinct change in the incidence of detected SCAD types and localizations over the last 25 years. SCAD type 2 and lesions in side branches were increasing, whereas SCAD type 1 and lesions in the LMCA and proximal segments were detected less frequently. Furthermore, shorter lesions with fewer involved segments were found in the last years. Hence, the increasing incidence of SCAD was based on higher rates of more subtle lesions. These findings might be the consequence of better spatial resolutions of the image converters and a higher familiarity of interventionalists with the presence and angiographic appearance of SCAD. Intravascular imaging such as optical coherence tomography and intravascular ultrasound was implemented only in a minority of cases. It might be assumed that the potential propagation of SCAD or iatrogenic dissection of the vulnerable coronary vessels in these patients [23] led the involved interventionalists to this low use despite better availability over time. Since there is the hypothesis that SCAD arises from an intramural hematoma with consecutive rupture of the intimal layer [9], the finding of more type 2 lesions in the recent years might also be a consequence of earlier diagnosis. However, the time point of presentation of patients after symptom onset did not differ in the analyzed period, which rather suggests that intimal rupture can appear independently from an intramural hematoma in a proportion of patients.

4.2. Presentation of patients

Despite changes in angiographic findings, the clinical presentation of patients did not change during the last 25 years. Baseline characteristics of the study population, with a majority of female patients and a median age around fifty years, were comparable to those of other studies [4–6,24]. Half of the SCAD patients presented with STEMI. This rather high rate might be the consequence of an underdiagnosis of NSTEMI in this population with predominantly female patients. It is known that women with typical symptoms of ACS are less likely to receive a diagnostic workup than men [25,26], especially in the absence of ECG changes. The same reasons might explain the rather high rate of men in this collective. The severity of cardiac function impairment, measured by Killip class, LVEF, LVEDP, and peak values of cardiac biomarkers were stable during the study period. This implies an increased incidence of both mild and severe cases of SCAD.

Most of the patients had detectable associated conditions and trigger factors, which confirms other published data [4,27]. Their prevalence did not change, and the proportion of patients with FMD was lower than in other published collectives [4,6,28,29]. FMD is likely underdiagnosed in this study collective, since screening for FMD was not performed routinely during the first years of the study period as a part of clinical management. However, it is unclear, if there is a lower prevalence of FMD in Switzerland, since data about this issue are lacking. One-third of patients have been found to suffer from migraine, which is within the range of previously published data [4,5,28]. There was an increasing trend of migraine and other neurologic disorders, however, based on a

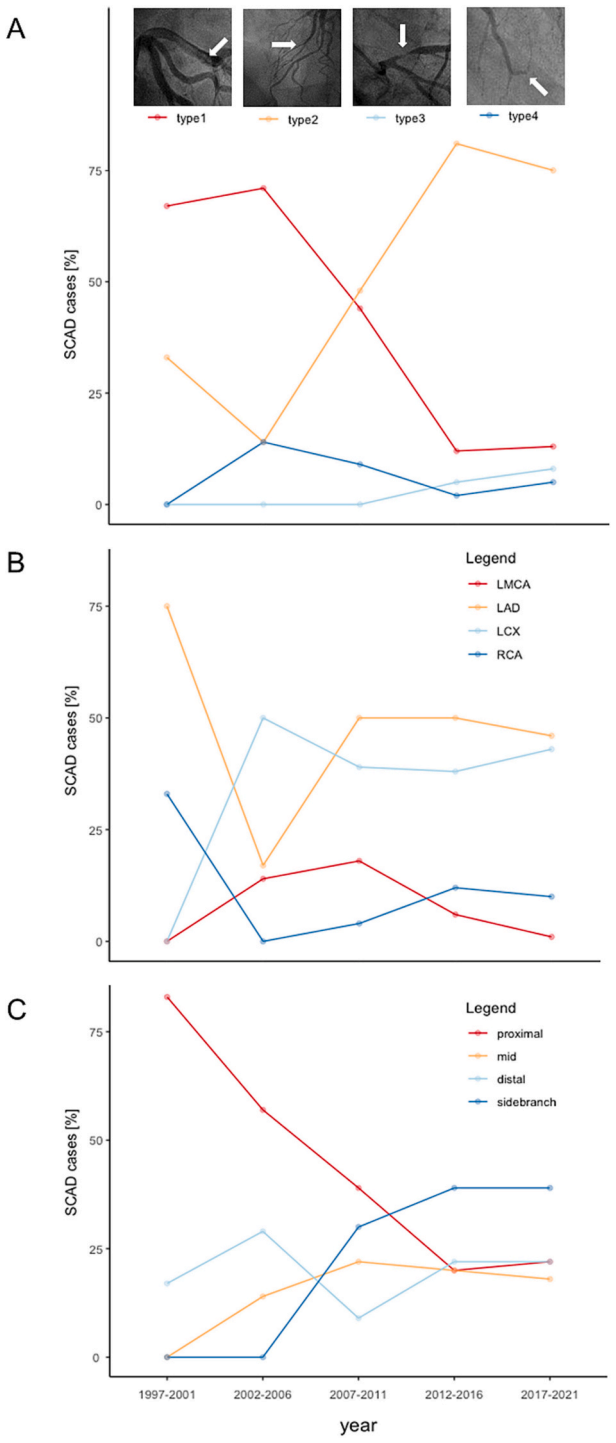

Fig. 2. Types of SCAD, affected vessels and segments. A, Proportions of SCAD types changed significantly over the study period. The increasing number of SCAD was a consequence of more SCAD type 2, which significantly increased over the study period ($p < 0.001$). The proportion of type 1 significantly decreased relatively to the total number of SCAD ($p < 0.001$). Arrows: region of SCAD lesion. B, SCAD lesions in LAD and LCX increased significantly over the study period ($p = 0.046$), whereas there was a decrease of lesions in the LMCA and RCA ($p = 0.017$). C, significantly more SCAD lesions were found in side branches of the coronary arteries over time ($p = 0.014$). The proportion of lesions in proximal segments decreases significantly ($p < 0.001$).

low rate in the early years of the study period. The amount of pregnancy-associated SCAD was stable and comparable to other studies [4,30,31]. Pregnancy has early been recognized as an associated condition in SCAD, which might be the reason that most cases of pregnancy-associated SCAD have been diagnosed correctly since the beginning of the study period. Of note, the association of exogenous hormones and recreational drugs with SCAD is only based on case reports [32–35] and the correlation of systemic inflammatory diseases with SCAD has been questioned following a recent retrospective case-control study [19].

4.3. Management

Median hospital stay was stable over time. A relatively long stay was common, which is currently recommended due to a relevant risk of SCAD progression or early recurrence [18,20]. However, the need for intensive care treatment, especially mechanical circulatory and respiratory support, was decreasing over time. Less severe in-hospital courses might be caused by changes in the revascularization strategies for SCAD. Most patients were treated conservatively nowadays, and the proportion of interventionally treated patients decreased. This development is in line with the recommendation of conservative treatment in stable patients without ongoing ischemia or high-risk anatomy, following the spontaneous healing and high risk of complications in PCI [18,20]. However, PCI was not performed exclusively in high-risk anatomical lesions, likely since this study mainly covered a period before this recommendation in the ACC/AHA scientific statement [18]. Except the above-mentioned recommendation of revascularization in high-risk anatomical lesions, there are no data available, if certain types or locations of SCAD lesions might benefit from an interventional treatment. Likewise, no changes could be found in lesions and types of SCAD that were selected for interventional management. Favorable in-hospital outcomes, with fewer patients treated on intensive care units despite stable cardiac biomarkers over time, suggest a positive effect of conservative treatment in SCAD.

The optimal pharmacological therapy has still not been elucidated. Only one observational study has shown a benefit of betablockers and optimal control of hypertension [36]. Correspondingly, pharmacological therapy did not change over time in this study and was mainly based on the recommendations for atherosclerotic ACS [37]. One recent retrospective study pointed to potential harm of dual antiplatelet therapy compared with single antiplatelet therapy [10]. However, these findings were not yet implemented in the clinical management of the patient collective studied.

4.4. Outcome

Patients had a substantial rate of death and other complications during the acute phase and follow-up. Mortality was notable and even higher than in atherosclerotic ACS [38]. However, the proportion of patients with death and other MACE was higher than in previously published collectives that focused on short-term outcomes [4,24], and the high number of MACE was mostly driven by SCAD recurrence and progression.

Overall MACE as well as proportions of patients with SCAD recurrence or progression, MI of any other cause, stroke, cardiac arrest, and death did not change within the study period. Stable rates of SCAD recurrences might be the consequence of unchanged medical therapy, since most recurrences appeared in other segments than first SCAD and might not be affected by the chosen revascularization therapy. The MACE rate in this study is higher than reported in previous publications [6,12,39,40]. The lower rates in other studies are explained by exclusion of SCAD progression and cardiac arrest in the MACE definition of these collectives. Slightly higher rates of the other complications might be an effect of the high rate of PCI. However, available retrospective data about impact of PCI on clinical outcomes are conflicting [41–43].

Most patients had a normal LVEF during follow-up, which is

Table 4
Management and Outcomes [N (%)].

	1997–2001		2002–2006		2007–2011		2012–2016		2017–2021		Total		P-value[a]
Hospitalization Duration [Days, median (IQR)]	11	(5, 18)	5	(3, 7)	5	(2, 11)	5	(3, 10)	6	(3, 9)	5	(3, 10)	0.848
Intensive Care Treatment													
Mechanical Support	1	(17)	1	(14)	5	(22)	0	(0)	3	(4)	10	(6)	**0.010**
Respiratory Therapy	2	(33)	1	(14)	7	(30)	5	(12)	8	(10)	23	(15)	**0.027**
Vasoactive Therapy	2	(33)	2	(29)	7	(30)	4	(10)	9	(11)	24	(15)	0.074
Total	2	(33)	2	(29)	8	(35)	5	(12)	10	(13)	27	(17)	**0.017**
Initial Management Strategy													
Conservative	2	(33)	0	(0)	11	(48)	26	(63)	61	(77)	100	(64)	**<0.001**
CABG	1	(17)	2	(29)	2	(9)	0	(0)	1	(1)	6	(4)	**0.001**
PCI	3	(50)	5	(71)	11	(48)	15	(37)	18	(23)	52	(33)	**0.002**
Pharmacological Therapy													
SAPT	0	(0)	1	(14)	2	(9)	4	(10)	5	(6)	12	(8)	0.814
DAPT	4	(67)	5	(71)	16	(70)	32	(78)	54	(68)	111	(71)	0.860
OAC	1	(17)	0	(0)	0	(0)	0	(0)	2	(3)	3	(2)	0.430
DAT/TAT	0	(0)	1	(14)	4	(17)	3	(7)	13	(17)	21	(14)	0.412
ACEI/ARB	5	(100)	4	(57)	20	(91)	32	(80)	54	(70)	115	(76)	0.112
Betablockers	5	(100)	5	(71)	16	(73)	27	(68)	54	(70)	107	(71)	0.358
MRA	0	(0)	0	(0)	0	(0)	2	(5)	3	(4)	5	(3)	0.357
CCB	0	(0)	0	(0)	4	(18)	12	(30)	9	(12)	25	(17)	0.885
Statin	3	(60)	4	(57)	19	(86)	22	(55)	46	(60)	94	(62)	0.326
Outcome													
MACE	2	(33)	1	(14)	7	(30)	13	(32)	15	(19)	38	(24)	0.312
Recurrence	1	(17)	0	(0)	2	(9)	5	(12)	3	(4)	11	(7)	0.284
Progression	0	(0)	0	(0)	1	(4)	3	(7)	4	(5)	8	(5)	0.542
Other MI	0	(0)	1	(14)	1	(4)	3	(7)	3	(4)	8	(5)	0.690
Cardiac Arrest	0	(0)	0	(0)	2	(9)	2	(5)	2	(3)	6	(4)	0.722
Stroke	0	(0)	0	(0)	0	(0)	1	(2)	0	(0)	1	(1)	0.890
Death	1	(17)	0	(0)	1	(4)	2	(5)	3	(4)	7	(5)	0.465
Follow-up LVEF													
≥ 50%	3	(60)	4	(80)	13	(87)	33	(92)	64	(87)	117	(87)	0.271
41–49%	0	(0)	0	(0)	2	(13)	2	(5)	7	(9)	11	(8)	0.501
≤ 40%	2	(40)	1	(20)	0	(0)	1	(3)	3	(4)	7	(5)	**0.012**

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CCB, calcium channel blocker; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; IQR, interquartile range; MACE, major adverse cardiovascular events; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy; TAT, triple antithrombotic therapy.

[a] P-values calculated using Mann-Kendall trend test for absolute numbers and Mantel-Haenszel test for proportions of the total numbers.

consistent with other published data [44]. A trend to a lower proportion of patients with persisting severely reduced LVEF is in line with the lower need of intensive care treatment over time in this study, and might hint towards an improved management of patients, even if MACE rates are not yet affected.

4.5. Study limitations

Several limitations have to be mentioned for this study. First, it is important to consider the mostly retrospective nature of the analysis. SCAD patients were identified during clinical management and not by retrospective review of all performed coronary angiograms during the study period. Thus, the raising incidences cannot be interpreted as true population-based incidences of SCAD, but as changes in the diagnosis of SCAD. Therefore, the study demonstrates improved awareness and better diagnosis of the disease, rather than alterations of the nature of SCAD over time. The same applies to associated conditions and triggers, since those might not have been screened if the relation to SCAD was not yet established. However, patients were screened during follow-up for those comorbidities, whenever possible. Second, the study was performed in a monocentric manner in a tertiary referral-center, since local differences in screening methods and data acquisition might have biased the analysis in a multicentric approach. However, results might not be applicable to all local conditions of cardiovascular care. Finally, the absolute number of MACE was low in this study, which limits the significance of those outcome data in this study.

5. Conclusions

Consistent with a growing scientific interest, there was a remarkable rise in the incidence of SCAD over the last 25 years, and it represents an important cause of ACS, meanwhile. It is likely that SCAD was largely underdiagnosed in the past and improved diagnostic sensitivity thanks to better awareness and high-resolution imaging has led to an increased detection rate. Appropriately, there was a change in detected SCAD types and localizations with a rising number of more subtle lesions. A clear change in revascularization strategies, with a growing proportion of conservative management, and a lower need for intensive care treatment could be shown over the last 25 years. A decreasing need for intensive care treatment despite stable cardiac biomarkers over time suggests a positive effect of conservative management. However, there was a constant high rate of MACE during follow-up that might be more affected by medical therapy. There is a need for the development of improved secondary prevention concepts. Further research effort and education are important to obtain a better impression of the disease and generate a better familiarity with this entity of ACS among physicians.

Disclosures

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