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CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry

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Aims The role of antiplatelet therapy in patients with spontaneous coronary artery dissection (SCAD) undergoing initial conservative management is still a matter of debate, with theoretical arguments in favour and against its use. The aims of this article are to assess the use of antiplatelet drugs in medically treated SCAD patients and to investigate the relationship between single (SAPT) and dual (DAPT) antiplatelet regimens and 1-year patient outcomes.

Methods and results We investigated the 1-year outcome of patients with SCAD managed with initial conservative treatment included in the DIssezioni Spontanee COronariche (DISCO) multicentre international registry. Patients were divided into two groups according to SAPT or DAPT prescription. Primary endpoint was 12-month incidence of major adverse cardiovascular events (MACE) defined as the composite of all-cause death, non-fatal myocardial infarction (MI), and any unplanned percutaneous coronary intervention (PCI). Out of 314 patients included in the DISCO registry, we investigated 199 patients in whom SCAD was managed conservatively. Most patients were female (89%), presented with acute coronary syndrome (92%) and mean age was 52.3 ± 9.3 years. Sixty-seven (33.7%) were given SAPT

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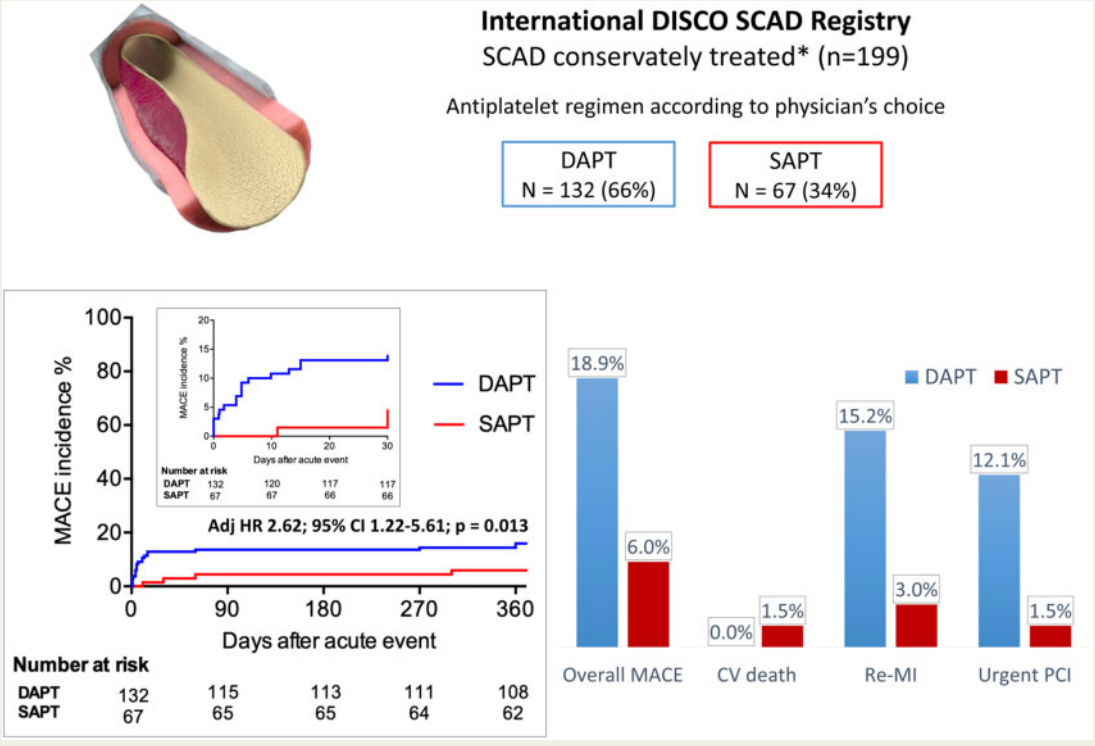
whereas 132 (66.3%) with DAPT. Aspirin plus either clopidogrel or ticagrelor were prescribed in 62.9% and 36.4% of DAPT patients, respectively. Overall, a 14.6% MACE rate was observed at 12 months of follow-up. Patients treated with DAPT had a significantly higher MACE rate than those with SAPT [18.9% vs. 6.0% hazard ratios (HR) 2.62; 95% confidence intervals (CI) 1.22–5.61; P = 0.013], driven by an early excess of non-fatal MI or unplanned PCI. At multiple regression analysis, type 2a SCAD (OR: 3.69; 95% CI 1.41–9.61; P = 0.007) and DAPT regimen (OR: 4.54; 95% CI 1.31–14.28; P = 0.016) resulted independently associated with a higher risk of 12-month MACE.

Conclusions In this European registry, most patients with SCAD undergoing initial conservative management received DAPT. Yet, at 1-year follow-up, DAPT, as compared with SAPT, was independently associated with a higher rate of adverse cardiovascular events (ClinicalTrial.gov id: NCT04415762).

Graphical Abstract



Thirty–day and 12–month impact of different antiplatelet regimens on spontaneous coronary artery dissection conservatively treated as first treatment strategy following angiographic diagnosis of spontaneous coronary artery dissection. The cumulative hazard curve for major adverse cardiac events at 12 months and 30 days were depicted in the lower left part of the figure. Twelve-month incidence of major adverse cardiac events, cardiovascular death, myocardial infarction, and unplanned PCI in both two groups was represented in the lower right part. SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy. In the upper panel is depicted the same curve focusing in the first 3 months. *Defined as conservative medical treatment as first strategy following angiographic diagnosis of SCAD. Among those, three cases in which no APT was administered because of clinical drawback or allergy were not included in the final analysis.

Keywords Spontaneous coronary artery dissection • Acute coronary syndrome • Antiplatelet therapy • Coronary artery disease

Introduction

Spontaneous coronary artery dissection (SCAD) is an increasingly diagnosed cause of acute coronary syndrome (ACS), particularly in women.[1–5] Its real incidence is probably even higher than reported: indeed, it has been under-diagnosed for years due to the lack of modern diagnostic tools (e.g. intravascular imaging) and low awareness of the disease.[6,7] Observations collected from contemporary SCAD case series have led to the general consensus that conservative therapy should be considered as a first-line approach in the absence of

clinical high-risk features[8–12]: dissections can resolve spontaneously over time after conservative management due to recollection of the intimal flap or resorption of the intramural haematoma (IMH).[13,14] Scarce data, however, are available regarding the type of medical treatment in such patients, who generally lack underlying atheroma. The choice of optimal antiplatelet therapy (APT) remains an unmet need. On the one hand, powerful platelet inhibition may worsen intramural haemorrhage; on the other hand, it may reduce the thrombotic risk linked to sub-endothelium exposure to flowing blood and reduce shear-mediated platelet activation that occurs at the sites of critical true lumen narrowing.[3] As a result, some degree of APT is to date considered helpful in SCAD.

However, the appropriate type and duration of APT have yet to be defined. Because of bleeding concerns, some authors suggest the use of clopidogrel[15] in the dual APT (DAPT) regimen, although ACS guidelines (without making a special case for SCAD) recommend a 12-month therapy with a stronger P2Y12 inhibitor for all ACS.[16,17] A possible correlation between different antiplatelet regimens and clinical outcomes in SCAD is lacking and no study has, to date, evaluated this issue.

Thus, the aim of the present analysis was to evaluate the safety of DAPT vs. single APT (SAPT) in medically managed patients with SCAD.

Methods

Patient population

DISCO (DIssezioni Spontanee COronariche) IT/SPA (ClinicalTrials.gov id: NCT04415762) is an observational, international, multicentre, retrospective registry that enrolled SCAD patients from 23 centres in Italy and Spain (see participating centres in Supplementary material online, *Appendix*).

All patients discharged with a diagnosis of non-atherosclerotic SCAD and aged >18 years were enrolled in the registry from 1 January 2009 to 31 December 2019. The diagnosis of SCAD was further confirmed by the core lab organized for this study by the co-ordinating centre. For the present analysis, we identified in the registry all cases satisfying the following inclusion criteria: (i) conservative medical treatment as the first strategy following angiographic diagnosis of SCAD and (ii) availability of data on prescribed APT. Patients were divided into two groups according to the antiplatelet regimen prescribed after the angiographic diagnosis of SCAD: (i) SAPT (with either aspirin 100 mg or a P2Y12 inhibitor) and (ii) DAPT (with aspirin 100 mg plus a P2Y12 inhibitor).

Data collection

Demographics, clinical presentation, treatment modality, angiographic findings, administered drugs, and early and late outcomes were extracted from the hospital databases of each centre. In case of missing data, the general practitioner or the patient himself was contacted or an in-person visit was scheduled to obtain the information needed. A dedicated electronic case report form (eCRF) was properly designed on the Cardiogroup.org research website. Data from each site were entered into the eCRF and the co-ordinating centre (Rivoli-Orbassano) generated the analysis reported in this manuscript. A dedicated data manager (Luca Lo Savio (L.L.S.)) was in charge of source verification, quality control, and queries generation from the co-ordinating centre to the participating sites in order to minimize bias. Follow-up data were collected by each centre through a review of medical records or during outpatient visits and/or telephone contacts. The study was approved by the institutional review committees and conducted in accordance with the Declaration of Helsinki; an informed consent to be submitted to the patient and an information letter addressed to the general practitioners were drawn up.

Angiographic analysis

All coronary angiograms were reviewed by a core laboratory involving the co-ordinating centre (Rivoli-Orbassano) and the leading recruiting centre of the study (Madrid). Angiograms were first sent to the co-ordinating centre and reviewed by two experienced interventional cardiologists (G.Q. and C.R.) to confirm the diagnosis of SCAD and angiographic type. In this phase, the cardiologists were blinded to clinical data and scan timepoint. In case of disagreement, consensus was achieved after discussion with a 3rd interventional cardiologist (Francesco Tomassini (F.T.)). Additional angiograms performed during the index hospitalization or follow-up as well as any intracoronary imaging available were also reviewed to improve diagnostic accuracy. After a confirmed diagnosis of SCAD at the co-ordinating centre, the angiographic classification was performed in a 2nd stage by both the Italian (G.Q., C.R., and E.C.) and the Spanish centre (R.M., F.M., and J.E.), with a previous consensus agreement on the specific criteria to be used, as well as subsequent online meetings to discuss unclear cases. All cases with concomitant presence of significant atherosclerotic disease (≥50% diameter stenosis) in other coronary arterial segments or with an underlying complicated plaque as revealed by intracoronary imaging were excluded from the present registry.

Definitions and outcomes

Spontaneous coronary artery dissection was classified according to the angiographic classification reported previously.[1,18] Briefly, type 1 was an angiographic radiolucent 'flap' and linear double lumen often associated with contrast hold-up; type 2 was a long (>20 mm) diffuse and smooth stenosis divided into type 2a where there is recrudescence of a normal calibre distal vessel and type 2b where the stenosis extends angiographically to the end of the vessel. Type 3 pattern was defined as focal angiographically indistinguishable from a focal atherosclerotic stenosis requiring diagnostic confirmation by intracoronary imaging. A complete occlusion pattern was defined as type 4. For diagnosing angiotype 4, the presence of other typical angiographic characteristics (angiotype 1 and 2), visible at the time of the baseline injections, during the percutaneous coronary intervention (PCI) or in surveillance angiograms, was necessary to establish the diagnosis of SCAD when intracoronary imaging was not used.

During the diagnostic process, in the case of recurrent SCAD, it was specified whether it was on the same segment or on another one. According to recent data,[14] spontaneous SCAD healing usually occurs within 30 days of the acute event in the majority of patients. Following this evidence, core-lab members decided to define 'recurrent SCAD' (i) a new SCAD in a different coronary vessel or (ii) a new SCAD of the same coronary vessel that occurred after 30 days.

The primary clinical outcome was (i) 12-month major adverse cardiovascular events (MACE)—a composite of all cause of death, non-fatal myocardial infarction (MI), and any unplanned revascularization (either percutaneous or surgical). Secondary endpoints were (i) in-hospital MACE; (ii) single MACE components both in hospital and at 12 months; and (iii) bleeding events at 12 months assessed according to the Bleeding Academic Research Consortium (BARC) classification.[19] Myocardial infarction was defined according to the 4th universal definition of MI.[20] In case of a confirmed or suspected adverse event, this was reported in a specific section of the eCRF. Coronary angiographies as well as available clinical information (clinical presentation, 12 lead electrocardiogram, troponin I values) were checked by the co-ordinating centre to adjudicate the event as MACE.

Statistical analysis

Categorical and binary variables were compared between groups using χ^2 tests. Continuous variables were compared using *t*-test, or Wilcoxon signed-rank test in case of non-normal distributions. For MACE and its components, time-to-event analyses were performed. Results are reported using hazard ratios (HR), 95% two-sided confidence intervals (CI), and cumulative hazard curves. Univariate and multivariable Cox regression analyses were used to identify independent predictors of MACE in the conservative treatment group. Variables related to clinical outcomes in univariate analysis ($P < 0.10$) were included in the multivariable model. Age and sex were included as background variables. A stepwise logistic regression model with an entry and exit level of significance of 0.10 was used to identify variables independently associated with MACE. A sensitivity analysis was performed excluding specific clinical or angiographic features considered at higher risk of events [age > 60 years; ≥3 cardiovascular risk factors; ST-elevation MI (STEMI) at presentation; ejection fraction <55%; angiographic type 2a SCAD] to identify potential factors that may influence the primary conclusion.

Statistical analyses were performed using SPSS 22.0 (IBM, Armonk, NY, USA), R-project statistical software, STATA 16.0 (StataCorp, College Station, TX, USA), and Graphpad Prism 4 (La Jolla, CA, USA). All tests were two-sided and *P*-values <0.05 were considered statistically significant.

Results

Study population

Overall, 314 patients were enrolled in the registry. Among them, 199 were managed conservatively and met the inclusion/exclusion criteria (*Figure 1*): 67 (33.7%) patients were treated with SAPT whereas 132 were prescribed DAPT (66.3%).

Baseline clinical and angiographic features are summarized in *Tables 1 and 2*. No relevant baseline or angiographic differences were present according to DAPT or SAPT treatment. The mean age of patients was 52.3 ± 9.3 years. There was a large representation of females (*n* = 177; 88.9%), more than a third of them (*n* = 70; 39.5%) in post-menopausal status. Conventional cardiovascular risk factors were found in a non-negligible number of patients: 39.7% had hypertension, 26.1% were current smokers, 37.2% had dyslipidaemia, and 3.0% diabetes. Anxiety and migraines were the most reported typical SCAD predisposing factors (31.2% and 20.1%, respectively). Overall, 109 patients (54.8%) did not report a precipitating factor associated with the acute event. Non-ST-elevation ACS (NSTE-ACS) was the most frequent admission diagnosis (*n* = 109; 54.8%), followed by STEMI (*n* = 74; 37.2%). The mean ejection fraction was 56.0 ± 7.8%. The left

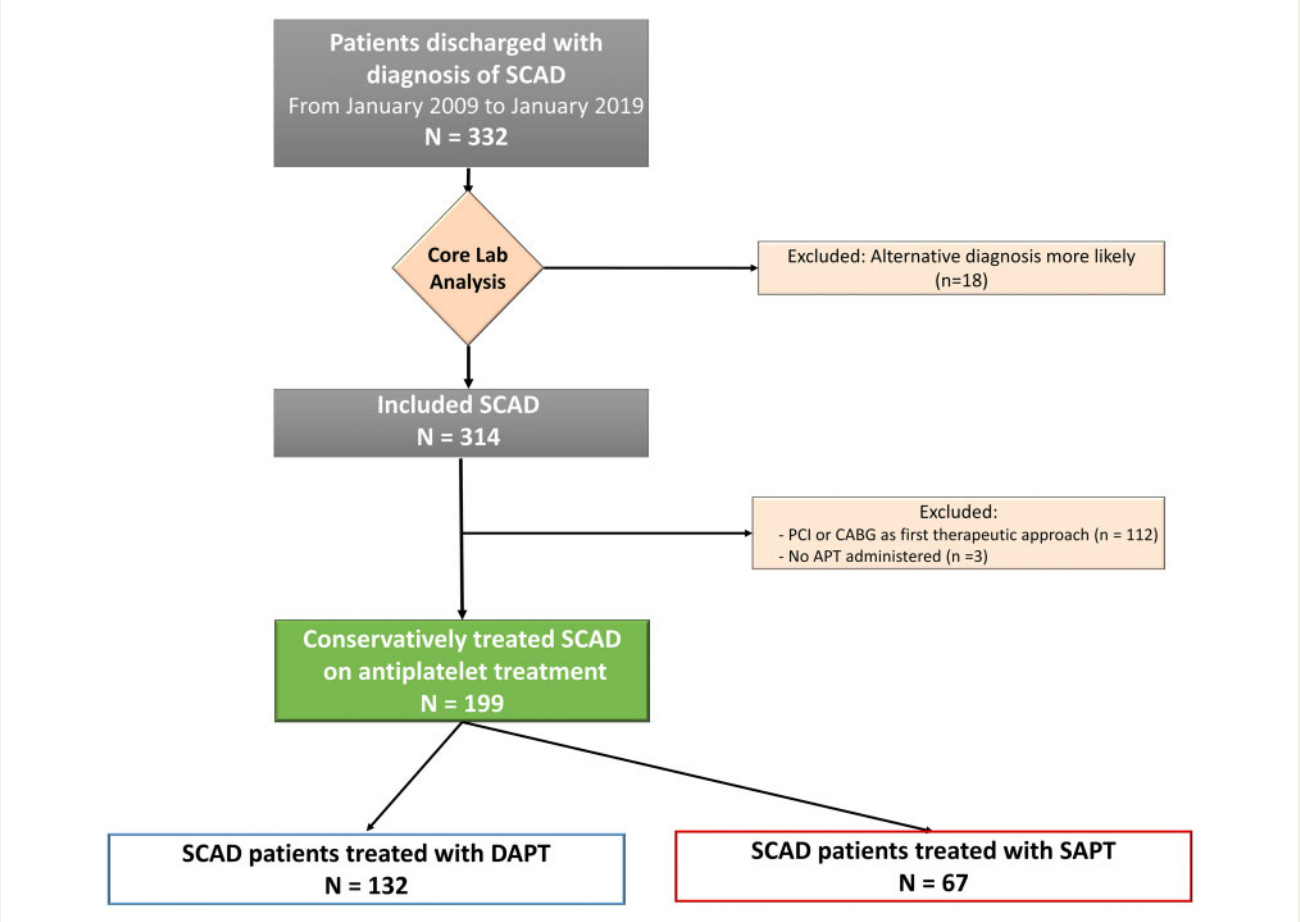


Figure 1 Study flow chart.

Table 1 Baseline characteristics

	Overall (*N* = 199)	DAPT (*N* = 132)	SAPT (N = 67)	*P*-value
Age (years)	52.3 ± 9.3	52.1 ± 8.9	52.7 ± 10.1	0.69
Female sex	177 (88.9)	116 (87.9)	61 (91.1)	0.5
T2DM	6 (3.0)	5 (3.9)	1 (1.5)	0.66
Insulin-dependent	1 (0.5)	1 (0.8)	0	
Dyslipidaemia	74 (37.2)	48 (36.4)	26 (38.8)	0.74
Hypertension	79 (39.7)	53 (40.2)	26 (38.8)	0.89
Current smoking	52 (26.1)	39 (29.5)	13 (19.4)	0.13
eGFR <30 mL/min	0	0	0	–
Previous MI	11 (5.5)	7 (5.3)	4 (4.5)	0.84
Previous PCI	5 (2.5)	4 (3.1)	1 (1.5)	0.53
Peripheral artery disease	4 (2.0)	3 (2.3)	1 (1.5)	0.71
Hypothyroidism	26 (13.1)	14 (10.6)	12 (17.9)	0.18
Menopausal at SCAD event	70/177 (39.5)	42/116 (36.2)	28/61 (45.9)	0.27
Previous cancer	6 (3.0)	1 (0.8)	5 (7.5)	0.02
Ongoing chemotherapy	0	0	0	–
Migraines	40 (20.1)	21 (15.9)	19 (28.3)	0.04
Depression	37 (18.6)	20 (15.2)	17 (25.3)	0.09
Anxiety	62 (31.2)	37 (28.0)	25 (37.3)	0.24
Hormonal therapy	24/177 (13.6)	14/116 (12.1)	10/61 (16.4)	0.46
Multiparity (≥3 pregnancies)	24/177 (13.6)	15/116 (12.9)	9/61 (14.7)	0.39
Clinical presentation				
STEMI	74 (37.2)	46 (35.4)	28 (42.4)	0.33
NSTE-ACS	109 (54.8)	74 (56.9)	35 (53.0)	0.61
Stable CAD	13 (6.5)	10 (7.7)	3 (4.5)	0.42
Others	3 (1.5)	2 (1.5)	1 (1.5)	1.00
Ejection fraction (%)	56.0 ± 7.8	56.0 ± 7.1	56.1 ± 8.9	0.97
Hospitalization length (days)	7,35 ± 5,31	6,99 ± 3,92	8,05 ± 4,46	0.42

CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; NSTE-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction; T2DM, type 2 diabetes mellitus.

anterior descending artery was the most frequently involved coronary artery (52.8%), followed by the left circumflex artery-obtuse marginal branch (26.7%) and the right coronary artery (19.3%). Multi-vessel SCAD was reported in 17 cases (8.5%) and angiographic type 2 SCAD was the predominant one with 120 cases (60.2%). Intracoronary imaging [intravascular ultrasound/optical coherence tomography (IVUS/OCT)] was performed in 20 patients (10.1%): in 16 cases (8.1%) only OCT was employed, in 2 (1.0%) cases only IVUS, whereas both OCT and IVUS were used in the last 2 cases (1.0%).

Drug management at discharge

In SAPT, aspirin 100 mg daily was the preferred antiplatelet drug in most cases (92.5%) with a lifelong indication in all cases. Cardiologists indicated clopidogrel (62.9%) or ticagrelor (36.4%) along with aspirin in DAPT regimens for 12 months in almost all cases (96.3%). In three cases, DAPT was prescribed for 6 months and in the other two cases for 18 and 24 months, respectively (*Figure 2*). In the DAPT group ($n = 132$), 46 (35.4%) patients presented with STEMI and 74 with NSTE-ACS (56.9%), whereas in the SAPT group ($n = 67$), 28 patients presented with STEMI (42.4%) and 35 with NSTE-ACS (53.0%). The choice of the antiplatelet regimen (DAPT or SAPT) was not different across ACS type (STEMI: 35.4% vs. 42.4%, $P = 0.33$; NSTE-ACS: 56.9% vs. 53.0%, $P = 0.6$).

No patient was on oral anticoagulation. All patients were treated with standard anticoagulation with heparin before the procedure and none was treated with glycoprotein IIb/IIIa inhibitor.

Statins were prescribed in 142 (71.3%) patients: their use was significantly higher in DAPT patients [108 (81.8%) in DAPT vs. 34 (50.7%) in SAPT, $P < 0.001$].

Details about drug management are provided in *Table 3*.

In-hospital outcome

More than a half of total MACEs ($n = 16$; 8.0%) occurred during hospitalization (1 death, 11 non-fatal MI, and 14 unplanned PCI). Mean hospitalization length was 7.35 ± 5.31 days (6.99 ± 3.92 in DAPT vs. 8.05 ± 4.46 in SAPT, $P = 0.42$). More in-hospital MACE occurred after treatment with two antiplatelet drugs (11.4% in DAPT vs. 1.5% in SAPT, $P = 0.016$, *Table 4*). The only death occurred in the SAPT group in a 49-year-old woman admitted after a resuscitated sudden prolonged cardiac arrest secondary to ventricular fibrillation:

Table 2 Angiographic and procedural features

	Overall (*N* = 199)	DAPT (*N* = 132)	SAPT (*N* = 67)	*P*-value
Coronary artery territory involved				
LM	1 (0.5)	0	1 (1.4)	0.32
LAD-DG	105 (52.8)	73 (55.3)	32 (47.8)	0.31
LCX-OM	54 (26.7)	37 (28.0)	17 (25.4)	0.69
RCA	39 (19.3)	22 (16.7)	17 (25.4)	0.14
Angiographic type				
Type 1	27 (13.7)	22 (16.8)	5 (7.5)	0.08
Type 2A	60 (30.1)	38 (29.0)	22 (32.8)	0.61
Type 2B	60 (30.1)	40 (30.5)	20 (29.8)	0.75
Type 3	13 (6.5)	10 (7.6)	3 (4.5)	0.39
Type 4	39 (19.6)	21 (16.0)	18 (26.9)	0.09
Multi-vessel SCAD	17 (8.5)	12 (9.1)	5 (7.4)	0.79
SCAD length (mm)	39.1 ± 22.9	37.2 ± 22.5	43.4 ± 23.7	0.18
TIMI flow				
TIMI 0	26 (13.2)	14 (10.7)	12 (17.9)	0.16
TIMI 1	15 (7.6)	9 (6.9)	6 (8.9)	0.61
TIMI 2	40 (20.3)	30 (23.1)	10 (14.9)	0.18
TIMI 3	116 (58.9)	77 (59.3)	39 (58.2)	0.89
Radial approach	169 (83.6)	109 (82.6)	57 (85.1)	0.66
Intracoronary imaging	20 (10.1)	14 (10.6)	6 (8.9)	0.71
IVUS use only	2 (1.0)	1 (0.7)	1 (1.5)	0.49
OCT use only	16 (8.1)	12 (9.1)	4 (5.9)	0.41
OCT + IVUS use	2 (1.0)	1 (0.7)	1 (1.5)	0.49
Planned angiographic FU	45 (22.6)	29 (22.0)	16 (23.9)	0.76
Complete SCAD healing	21 (10.5)	12 (9.1)	9 (13.4)	0.34
Planned CCTA	7 (3.5)	4 (3.0)	3 (4.5)	0.69

DG, diagonal branch; LAD, left anterior descending; LCX, left circumflex artery; LM, left main; RCA, right coronary artery; SCAD, spontaneous coronary artery dissection; TIMI, thrombolysis in myocardial infarction.

coronary angiography showed an SCAD involving the left coronary circumflex and the patient died 20 days after hospital admission due to irreversible hypoxic encephalopathy. Recurrent SCAD occurred in 12 (6.0%) patients, with 6 of them within 6 months after discharge.

Twelve-month outcome

Follow-up was available in 199 (100%) patients after discharge. A total of 197 patients (99.0%) were followed up for ≥6 months, and 194 (98.0%) for ≥12 months. The mean follow-up was 11.8 ± 1.3 months. In 52 (25.7%) patients, a scheduled surveillance coronary angiography was performed to confirm SCAD healing after the conservative approach (*Figure 3*) or to evaluate the long-term result of bail-out PCI indicated for failed medical management of SCAD (*Figure 4*). At 12 months, 29 patients (14.6%) experienced an MACE: 1 death, 22 non-fatal MI, and 17 unplanned PCI. Dual antiplatelet therapy was associated with a higher 1-year MACE rate compared with SAPT (18.9% vs. 6.0%; HR 2.62, 95% CI 1.22–5.61, $P = 0.013$). Both non-fatal MI (15.2% vs. 3.0%; HR 3.20, 95% CI 1.33–7.69, $P = 0.009$) and unplanned PCI (12.1% vs. 1.5%; HR 3.69, 95% CI 1.36–9.91, $P = 0.01$) mostly occurred early within the 1st month and contributed to this excess in MACE (*Graphical abstract*, *Table 4*, and Supplementary material online, *Appendix Figure SA*). Details of all reported adverse events are provided in Supplementary material online, *Appendix Table SA* .

At 12 months, bleeding events occurred in 15 (7.5%) patients [12 (9.1%) in DAPT vs. 3 (4.5%) in SAPT; $P = 0.24$]. Of these, two bleeding events occurred in the hospital, both in the DAPT group. All events were classified as minor bleeding: 10 BARC 1 and 5 BARC 2 (*Table 4*). Twelve (6.0%) patients experienced recurrent SCAD, with 6 of them within 6 months after discharge: 10 patients (7.6%) were on DAPT whereas 2 (3.0%) on SAPT with no significant difference between them ($P = 0.2$; Supplementary material online, *Appendix Table SB*).

At multivariable Cox regression analysis, type 2a SCAD (HR 3.69; 95% CI 1.41–9.61; $P = 0.007$) and DAPT regimen (HR 4.54; 95% CI 1.31–14.28; $P = 0.016$) were independent predictors of 12-month MACE (*Figure 5*). The proportionality assumptions were checked graphically by plotting the log cumulative hazard vs. (log) time at follow-up and by applying a test based on Schoenfeld residuals that failed to reject the null hypothesis that event rate was affected by time ($P = 0.702$).

The cumulative hazard curves for any composite outcome (Supplementary material online, *Figure SA*) as well as an additional MACE-survival analysis curve up to 24 months (Supplementary material online, *Figure SB*) are reported in the Supplementary material online, *Appendix*.

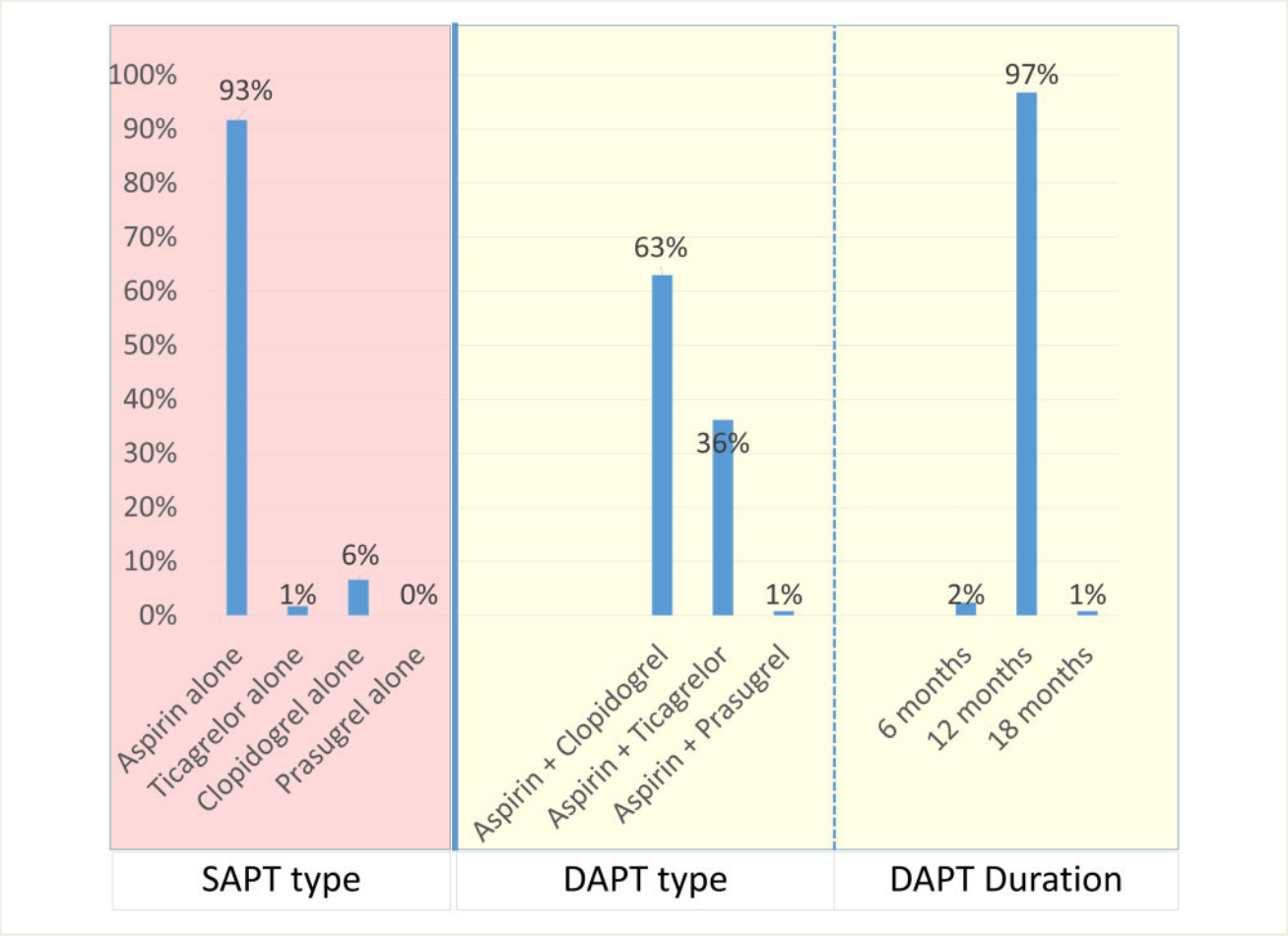


Figure 2 Type and duration of antiplatelet therapy in conservatively managed patients with spontaneous coronary artery dissection. DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

The results of sensitivity analyses were consistent with those from the primary analysis leading to similar conclusions (Supplementary material online, *Appendix Table SC*).

Discussion

The main results obtained from our study are the following: (i) in contemporary clinical practice, most patients with SCAD undergoing initial conservative management receive antiplatelet treatment, with DAPT prescribed in two-thirds of cases; (ii) at 12 months, DAPT is associated with a higher MACE rate compared with SAPT, mainly driven by an early excess of non-fatal MI or unplanned PCI; and (iii) DAPT and angiographic type 2a SCAD are independently associated with worse outcome (*Graphical abstract*).

Advancements in the knowledge of the causes and clinical evolution of SCAD largely rely on the analysis of large series of patients reflecting a palette of pathological substrates, clinical presentations, and therapeutic attitudes. This approach was applied also to our research, which provides a snapshot on the antithrombotic strategies in patients with conservatively treated SCAD. Dual antiplatelet therapy, particularly aspirin plus clopidogrel, was the most common APT used in SCAD patients from the participating centres of this study. These data are in keeping with those observed in non-European countries in the largest prospective SCAD cohort reported to date[21] and in other large contemporary series.[15,22,23] Overall, more than two-thirds of conservatively managed patients are discharged on DAPT, usually extended up to 12 months, and statin, regardless of the unconventional type of ACS. Existing evidence and guidelines on ACS strongly support DAPT with a potent P2Y12 inhibitor, regardless of the management strategy adopted (PCI or conservative).[24–26] Conversely, the benefit of any APT in conservatively managed SCAD is uncertain and controversial. The American and European position statements on SCAD management[1,2] do not recommend firmly APT regimens for medically managed patients and cast doubts on the benefit of DAPT. However, given the lack of evidence, it seems reasonable to at least avoid potent P2Y12 inhibitors.

The antithrombotic effect of antiplatelet agents may enhance intramural bleeding causing propagation of the dissection and subsequent events, as well as it may cause a delay in the natural resorption of IMH.[4] On the other hand, the presence of a thrombus in the true lumen of spontaneously dissected vessels has been documented in

Table 3 Drugs administered

	DAPT (*N* = 132)	SAPT (*N* = 67)	*P*-value
Aspirin alone	—	62 (92.5)	—
Ticagrelor alone	—	1 (1.5)	—
Clopidogrel alone	—	4 (5.9)	—
Prasugrel alone	—	0	—
Aspirin + clopidogrel	83 (62.9)	—	—
Aspirin + ticagrelor	48 (36.4)	—	—
Aspirin + prasugrel	1 (0.7)	—	—
Antiplatelet therapy duration			
6 months	3 (2.3)	—	—
12 months	127 (96.3)	—	—
18 months	1 (0.7)	—	—
24 months	1 (0.7)	—	—
Lifelong indication	0	67 (100%)	—
Beta-blocker	109 (82.6)	48 (71.6)	0.12
Calcium-antagonist	14 (10.6)	7 (10.4)	0.97
Statin	108 (81.8)	34 (50.7)	<0.001

Aspirin was administered 100 mg daily, ticagrelor 90 mg twice daily, and prasugrel 10 mg daily.

Table 4 In-hospital and 1-year major adverse cardiovascular events

	Overall (*N* = 199)	DAPT (*N* = 132)	SAPT (*N* = 67)	*P*-value
In-hospital events				
Overall MACE	16 (8.0)	15 (11.4)	1 (1.5)	0.016
All-cause death	1 (0.5)	0	1 (1.5)	—
Non-fatal MI	11 (5.5)	11 (8.3)	0	—
Any unplanned PCI	14 (7.0)	14 (10.6)	0	—
Bleeding	2 (1.0)	2 (1.5)	0	—
BARC 1	1 (0.5)	1 (0.7)	0	—
BARC 2	1 (0.5)	1 (0.7)	0	—
12-month events				
Overall MACE	29 (14.6)	25 (18.9)	4 (6.0)	0.013
All-cause death	1 (0.5)	0	1 (1.5)	—
Non-fatal MI	22 (11.1)	20 (15.2)	2 (3.0)	0.009
Any unplanned PCI	17 (8.5)	16 (12.1)	1 (1.5)	0.010
Bleeding	15 (7.5)	12 (9.1)	3 (4.5)	0.24
BARC 1	10 (5.0)	7 (5.3)	3 (4.5)	1.00
BARC 2	5 (2.5)	5 (3.8)	0	—

MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

OCT studies[27,28] supporting a role for APT at least in the early stages of SCAD. Our results suggest that DAPT may be harmful in terms of safety compared with SAPT for conservatively managed patients, with an excess of Re-infarction and urgent revascularization occurring early after initial SCAD presentation. These findings support the hypothesis that a more potent APT may have deleterious effects in SCAD by inducing IMH propagation. Moreover, APT may cause menorrhagia in these patients who are ~90% women, with about half in the premenopausal state.[2] In this regard, in our population, 15 bleeding events occurred, of which 2 during hospitalization. Since the SCAD population is predominantly young, as expected all events reported were minor bleedings (75% BARC 1, 25% BARC 2), but a higher incidence of bleeding was reported in the DAPT group, though not significantly different from the SAPT group. Additionally, both in-hospital bleeding events were recorded in patients on DAPT.

The early occurrence of adverse events seen in our series (more than a half of the total within the 1st month) is an important finding that is in line with previous reports.[21,22,29] Recently, data on 30-day SCAD readmission rates were reported from a large nationwide readmission database in the USA.[30] Authors estimated a higher re-

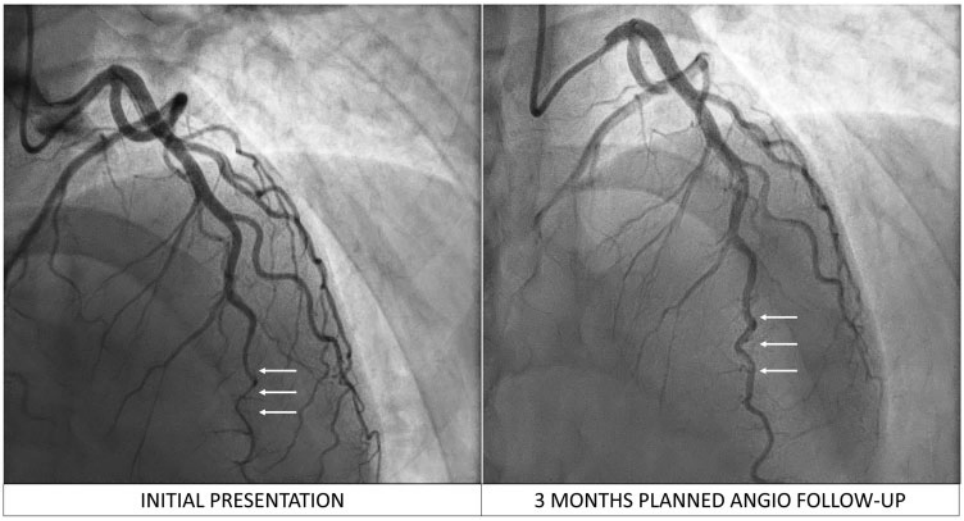


Figure 3 A 39-year-old woman, former smoker, presenting with ST-elevation myocardial infarction. (*A*) Index coronary angiography: type 2b spontaneous coronary artery dissection was present in the mid-distal left anterior descending artery. The patient was treated conservatively with aspirin and beta-blockers without subsequent in-hospital events. (*B*) At 3-month planned angiographic follow-up, the patient was asymptomatic with complete angiographic healing of left anterior descending artery spontaneous coronary artery dissection.

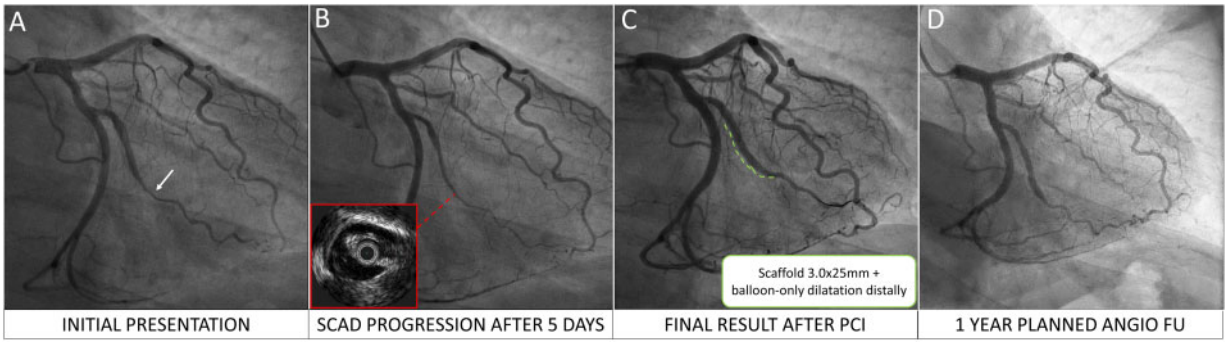


Figure 4 A 51-year-old woman without clinical risk factors presenting with non-ST-elevation myocardial infarction after an isometric exercise. (*A*) Index coronary angiography: type 2a spontaneous coronary artery dissection was present in the obtuse marginal branch. The patient was treated medically with dual antiplatelet therapy plus beta-blocker. (*B*) Five days later during the in-hospital stay, she complained of angina. Coronary angiography showed type 2b spontaneous coronary artery dissection and a TIMI flow 2. A wire was gently manipulated and advanced distally. Intravascular ultrasound pullback confirmed the presence of dissection and intramural haematoma compressing the true lumen. (*C*) Final angiographic result after balloon-only angioplasty distally and a 3.0 mm × 25 mm Magnesium Resorbable Scaffold (Magmaris) implantation in the dissected segment. Final TIMI flow 3 was obtained. The patients were discharged 5 days later. (*D*) At 1-year planned angiographic follow-up, the patient was asymptomatic with an excellent percutaneous coronary intervention result.

admission rate in SCAD compared with a non-SCAD ACS cohort (12.3% vs. 9.9%; $P = 0.022$) with the cardiac cause being the leading reason for re-hospitalization. This underscores the importance of close surveillance with prolonged monitoring of conservatively managed SCAD patients.[31]

A possible explanation for the association of early clinical SCAD progression with the deleterious effects of DAPT is the pathological substrate of a contained compressive IMH. The contained (not teared) IMH is thought to be caused by the rupture of vasa vasorum with subsequent micro-vessel haemorrhage in the lamina media ('outside-in' mechanism).[32] This hypothesis raised the concern that antithrombotic therapy in such patients may worsen intramural bleeding with further propagation and compression, ultimately resulting in clinical adverse progression. On the other hand, when an intimomedial tear communicating both lumens is present, a hypothetical drug-mediated increase of mural bleeding would not have such a clinical impact

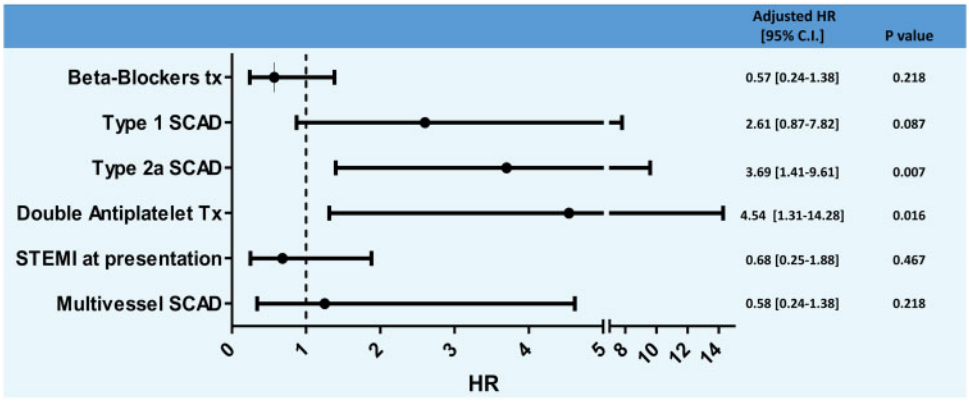


Figure 5 Independent predictors of major adverse cardiovascular events at 12-month follow-up in the study population. HR, hazard ratio; MACE, major adverse cardiovascular events.

because the haematoma would be released into the circulation. In a study by Waterbury *et al.*[29] on conservatively managed SCAD, angiographic presentation as 'pure' IMH entailed a greater risk of early clinical progression compared with the angiographic radiolucent 'flap' and linear double lumen (intimomedial tear with communication between false and true lumens) after adjusting for several confounders. García-Guimaraes *et al.*[22] reported similar findings from a large multicentre registry, in which type 2 SCAD, defined by the presence of long contained IMH (>20 mm), was found to be an independent predictor of in-hospital MACE. Interestingly, type 2a was independently related to MACE occurrence in our cohort, and DAPT was found to be an independent predictor of poor outcome in the same analysis. Taken together, our data seem to support the hypothesis that potent antithrombotic/APT may be harmful in conservatively managed SCAD patients, especially those with contained IMH.

Limitations

Although this is the largest European SCAD series reported so far, the sample size may have limited statistical power. This was an observational study analysing different treatment regimens with no randomization, which entails inherent limitations. Consequently, our results should be interpreted with caution and should be regarded as hypothesis generating. A number of limitations should be clearly acknowledged. First, the observational design is without a prior sample size calculation that may have limited statistical power. The choice of antiplatelet treatment was at the physician's discretion and could be potentially influenced by many clinical or angiographic features that we cannot identify. Consequently, the absence of randomization entails important limitations, as we cannot control all the potential baseline differences or residual confounders in the two study groups. Second, despite a systematic review of all cases in a dedicated core lab, some patients with atherosclerotic coronary artery disease could have been included given the limited use of intracoronary imaging to confirm SCAD diagnosis. Moreover, we cannot exclude a potential influence of the use of imaging tools on the antiplatelet regimen chosen. Third, despite a large data collection, some clinical and instrumental information is missing. Unfortunately, it was not possible to retrieve full information about all surface ECG performed during hospitalization and, consequently, to correlate the site of ischaemia detected on ECG with the PCI target vessel for all cases. Finally, as in any research focused on low-prevalence disease, the statistical power of multivariable analysis is limited by the low numbers of events. Consequently, our findings should be interpreted taking into consideration all the aforementioned issues, waiting for future research focused on this topic. We make a call for further research to elucidate the role of antithrombotic treatment in SCAD.

Conclusions

In medically treated SCAD patients, the risk of subsequent MI or unplanned coronary revascularization is not trivial and occurs mostly within the 1st month. Although DAPT is currently the most frequently adopted regimen in conservatively managed SCAD patients, we observed that DAPT entailed a more than two-fold increased risk of MACE compared with SAPT after 12 months of follow-up. Our findings should be interpreted with caution and warrant further confirmation. However, since APT in conservatively managed SCAD has remained unsupported by evidence so far, this study may inform cardiologists in their decision-making, which should always be individualized and guided by clinical judgement.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data that support the findings of this study are available on request from the corresponding author (E.C.).

References

1. Adlam D, Alfonso F, Maas A, Vrints C, Hussaini A. A, Bueno H, Capranzano P, Gevaert S, Hoole SP, Johnson T, Lettieri C, Maeder MT, Motreff P, Ong P, Persu A, Rickli H, Schiele F, Sheppard MN, Swahn E; Writing Committee. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J* 2018;**39**:3353–3368.
2. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, Ganesh SK, Gulati R, Lindsay ME, Mieres JH, Naderi S, Shah S, Thaler DE, Tweet MS, Wood MJ; American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation* 2018;**137**:e523–e557.
3. Saw J, Mancini GBJ, Humphries KH. Contemporary review on spontaneous coronary artery dissection. *J Am Coll Cardiol* 2016;**68**:297–312.
4. Al-Hussaini A, Adlam D. Spontaneous coronary artery dissection. *Heart* 2017;**103**:1043–1051.
5. Macaya F, Salinas P, Gonzalo N, Fernández-Ortiz A, Macaya C, Escaned J. Spontaneous coronary artery dissection: contemporary aspects of diagnosis and patient management. *Open Heart* 2018;**5**:e000884.
6. Rashid HNZ, Wong DTL, Wijesekera H, Gutman SJ, Shanmugam VB, Gulati R, Malaipan Y, Meredith IT, Psaltis PJ. Incidence and characterisation of spontaneous coronary artery dissection as a cause of acute coronary syndrome—a single-centre Australian experience. *Int J Cardiol* 2016;**202**:336–338.
7. Cerrato E, Giacobbe F, Rolfo C, Quadri G, Tomassini F, Ferrari F, Mariani F, Anselmino M, Bianco M, Belliggiano D, Savio LL, Franzé A, Barbero U, Porto I, Mejía-Rentería H, Macaya F, Salinas P, Gonzalo N, Escaned J, Montagna L, Varbella F. Role of invasive and non-invasive imaging tools in the diagnosis and optimal treatment of patients with spontaneous coronary artery dissection. *Curr Cardiol Rep* 2019;**21**:122.
8. Adlam D, García-Guimaraes M, Maas AHEM. Spontaneous coronary artery dissection: no longer a rare disease. *Eur Heart J* 2019;**40**:1198–1201.
9. Saw J. Natural history of spontaneous coronary artery dissection: to stent or not to stent? *EuroIntervention* 2019;**14**:1353–1356.
10. Tweet MS, Eleid MF, Best PJM, Lennon RJ, Lerman A, Rihal CS, Holmes DR, Hayes SN, Gulati R. Spontaneous coronary artery dissection: revascularization versus conservative therapy. *Circ Cardiovasc Interv* 2014;**7**:777–786.
11. Gilhofer TS, Saw J. Spontaneous coronary artery dissection: a review of complications and management strategies. *Expert Rev Cardiovasc Ther* 2019;**17**:275–291.
12. Buccheri D, Zambelli G, Alfonso F, Cortese B. Pulse on spontaneous coronary artery dissections: experience-based survey. *JACC Cardiovasc Interv* 2017;**10**:1469–1471.
13. Vanzetto G, Berger-Coz E, Barone-Rochette G, Chavanon O, Bouvaist H, Hacini R, Blin D, Machecourt J. Prevalence, therapeutic management and medium-term prognosis of spontaneous coronary artery dissection: results from a database of 11,605 patients. *Eur J Cardiothorac Surg* 2009;**35**:250–254.
14. Hassan S, Prakash R, Starovoytov A, Saw J. Natural history of spontaneous coronary artery dissection with spontaneous angiographic healing. *JACC Cardiovasc Interv* 2019;**12**:518–527.
15. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, Mancini GBJ. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol* 2017;**70**:1148–1158.
16. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
17. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
18. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. *Catheter Cardiovasc Interv* 2014;**84**:1115–1122.
19. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;**123**:2736–2747.
20. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group. Fourth Universal Definition of Myocardial Infarction (2018). *Eur Heart J* 2019;**40**:237–269.
21. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, Brass N, Lavoie A, Bishop H, Lavi S, Pearce C, Renner S, Madan M, Welsh RC, Lutchmedial S, Vijayaraghavan R, Aymong E, Har B, Ibrahim R, Gornik HL, Ganesh S, Buller C, Matteau A, Martucci G, Ko D, Mancini GBJ. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J* 2019;**40**:1188–1197.
22. García-Guimaraes M, Bastante T, Macaya F, Roura G, Sanz R, Barahona Alvarado JC, Tizón H, Flores-Ríos X, Moreu J, Ojeda S, Nogales JM, Veiga G, Masotti M, Camacho-Freire SJ, Jiménez-Valero S, Jiménez-Kockar M, Lozano Í, González-Ferreiro R, Velázquez M, Avanzas P, Rivero F, Alfonso F. Spontaneous coronary artery dissection in Spain: clinical and angiographic characteristics, management, and in-hospital events. *Rev Esp Cardiol (Engl Ed)* 2021;**74**:15–23.
23. Lettieri C, Zavalloni D, Rossini R, Morici N, Ettori F, Leonzi O, Latib A, Ferlini M, Trabattoni D, Colombo P, Galli M, Tarantini G, Napodano M, Piccaluga E, Passamonti E, Sganzerla P, Ielasi A, Coccato M, Martinoni A, Musumeci G, Zanini R, Castiglioni B. Management and long-term prognosis of spontaneous coronary artery dissection. *Am J Cardiol* 2015;**116**:66–73.
24. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
25. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, Smith PK. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2016 appropriate use criteria for coronary revascularization in patients with acute coronary syndromes: a report of the American College of Cardiology appropriate use criteria task force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2017;**69**:570–591.
26. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Investigators P. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
27. Alfonso F, Paulo M, Gonzalo N, Dutary J, Jimenez-Quevedo P, Lennie V, Escaned J, Bañuelos C, Hernandez R, Macaya C. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. *J Am Coll Cardiol* 2012;**59**:1073–1079.
28. Alfonso F, Canales E, Aleong G. Spontaneous coronary artery dissection: diagnosis by optical coherence tomography. *Eur Heart J* 2009;**30**:385.
29. Waterbury TM, Tweet MS, Hayes SN, Eleid MF, Bell MR, Lerman A, Singh M, Best PJM, Lewis BR, Rihal CS, Gersh BJ, Gulati R. Early natural history of spontaneous coronary artery dissection. *Circ Cardiovasc Interv* 2018;**11**:e006772.
30. Gad MM, Mahmoud AN, Saad AM, Bazarbashi N, Ahuja KR, Karrthik AK, Elgendy IY, Elgendy AY, Don CW, Hira RS, Massoomi MR, Saw J, Anderson RD, Kapadia SR. Incidence, clinical presentation, and causes of 30-day readmission following hospitalization with spontaneous coronary artery dissection. *JACC Cardiovasc Interv* 2020;**13**:921–932.
31. Quadri G, Cerrato E, Escaned J, Rolfo C, Tomassini F, Ferrari F, Mariani F, Varbella F. Importance of close surveillance of patients with conservatively managed spontaneous coronary artery dissection. *JACC Cardiovasc Interv* 2018;**11**:e87–e89.
32. Vrints CJM. Spontaneous coronary artery dissection. *Heart* 2010;**96**:801–808.