ESC European Society of Cardiology

European Heart Journal (2025) **00**, 1–12
https://doi.org/10.1093/eurheartj/ehaf097

CLINICAL RESEARCH
Ischaemic heart disease

The Australian-New Zealand spontaneous coronary artery dissection cohort study: predictors of major adverse cardiovascular events and recurrence

Quan M. Dang [1,*], Peter J. Psaltis [2,3,4], Sonya Burgess [5,6], Jaya Chandrasekhar[7,8], Swati Mukherjee [9], Leonard Kritharides [10,11,12], Nigel Jepson[13,14,15], Sarah Fairley[16], Abdul Ihdayhid [17,18], Jamie Layland[19,20], Richard Szirt[21], Seif El-Jack[22], Aniket Puri[23], Esther Davis[24,25], Imran Shiekh[26], Ruth Arnold[27], Monique Watts[28,29], Jessica A. Marathe[10,11,12], Rohan Bhagwandeen [30], Edwina Wing-Lun [5,31,32], Ravinay Bhindi[33], Tom Ford [34], Sidney Lo[35], Simone Marschner [1], and Sarah Zaman [1,36]

[1]Westmead Applied Research Centre, University of Sydney, Sydney, Australia; [2]Adelaide Medical School, The University of Adelaide, Adelaide, Australia; [3]Lifelong Health Theme, South Australian Health and Medical Research Institute, Adelaide, Australia; [4]Department of Cardiology, Central Adelaide Local Health Network, Adelaide, Australia; [5]University of Sydney, Sydney, Australia; [6]Department of Cardiology, Nepean Hospital, Sydney, Australia; [7]Department of Cardiology, Box Hill Hospital, Melbourne, Australia; [8]Eastern Health Clinical School, Monash University, Melbourne, Australia; [9]Department of Cardiology, Cabrini Hospital, Melbourne, Australia; [10]ANZAC Medical Research Institute, Sydney, Australia; [11]Sydney Medical School, University of Sydney, Sydney, Australia; [12]Department of Cardiology, Concord Repatriation General Hospital, Sydney, Australia; [13]Department of Cardiology, Prince of Wales Hospital, Sydney, Australia; [14]Prince of Wales Clinical School, University of New South Wales, Sydney, Australia; [15]Eastern Heart Clinic, Sydney, Australia; [16]Department of Cardiology, Wellington Hospital, Wellington, New Zealand; [17]Department of Cardiology, Fiona Stanley Hospital, Perth, Australia; [18]Harry Perkins Institute of Medical Research, Curtin Medical School, Curtin University, Perth, Australia; [19]Department of Cardiology, Frankston Hospital, Melbourne, Australia; [20]Peninsula Clinical School, Central Clinical School, Monash University, Melbourne, Australia; [21]Department of Cardiology, St George Hospital, Sydney, Australia; [22]Cardiovascular Unit, North Shore Hospital, Waitemata, New Zealand; [23]Department of Cardiology, Christchurch Hospital, Christchurch, New Zealand; [24]Victorian Heart Institute, Monash University, Melbourne, Australia; [25]Department of Cardiology, Victorian Heart Hospital, Melbourne, Australia; [26]Department of Cardiology, Royal Perth Hospital, Perth, Australia; [27]Orange Base Hospital, Orange, Australia; [28]Department of Cardiology, Alfred Hospital, Melbourne, Australia; [29]University of Melbourne, Melbourne, Australia; [30]Cardiology Department, John Hunter Hospital, Newcastle, Australia; [31]Department of Cardiology, Royal Darwin Hospital, Darwin, Australia; [32]Menzies School of Health Research, Darwin, Australia; [33]Department of Cardiology, Royal North Shore Hospital, Sydney, Australia; [34]The University of Newcastle Central Coast Clinical School, Gosford, Australia; [35]Department of Cardiology, Liverpool Hospital, Sydney, Australia; and [36]Department of Cardiology, Westmead Hospital, Sydney, Australia

Received 6 August 2024; revised 22 October 2024; accepted 4 February 2025

Abstract

Background and Aims Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of acute coronary syndrome (ACS). Recent data suggest a harmful association of dual antiplatelet therapy compared with single antiplatelet therapy following SCAD. This study investigated independent predictors of major adverse cardiovascular events (MACEs) and recurrence in patients with SCAD.

Methods This multicentre cohort study involving 23 Australian and New Zealand sites included patients aged ≥18 years with an ACS due to SCAD confirmed on core laboratory adjudication. Multivariable Cox proportional hazard models analysed predictors for the primary MACE outcome.

* Corresponding author. Email: quanmdang@gmail.com

Results Among 586 patients, 505 (150 prospective, 355 retrospective) with SCAD confirmed by core laboratory adjudication, mean age was 52.2 ± 10.6 years, 88.6% were female, and 74.5% were Caucasian. At long-term follow-up (median 21 months), MACE and SCAD recurrence occurred in 8.6% and 3.6% of patients, respectively. Oral anticoagulation on discharge [adjusted hazard ratio (aHR) 3.8, 95% confidence interval (CI) 1.6–9.3, $P = .003$], ticagrelor combined with aspirin (aHR 1.8, 95% CI 1.04–3.2, $P = .037$), fibromuscular dysplasia (aHR 2.2, 95% CI 1.05–4.5, $P = .037$), and history of stroke (aHR 3.8, 95% CI 1.2–12.2, $P = .03$) were independently associated with higher MACE. Fibromuscular dysplasia (aHR 3.9, 95% CI 1.5–26.5, $P = .01$), ticagrelor combined with aspirin (aHR 2.6, 95% CI 2.1–5.3, $P = .01$), and history of stroke (aHR 6.2, 95% CI 1.8–9.5, $P = .01$) were also associated with higher SCAD recurrence.

Conclusions The findings support the hypothesis that SCAD is primarily caused by intramural bleeding, with a harmful association of more potent antiplatelet therapy and anticoagulation with adverse cardiovascular outcomes.

Structured Graphical Abstract

Key Question

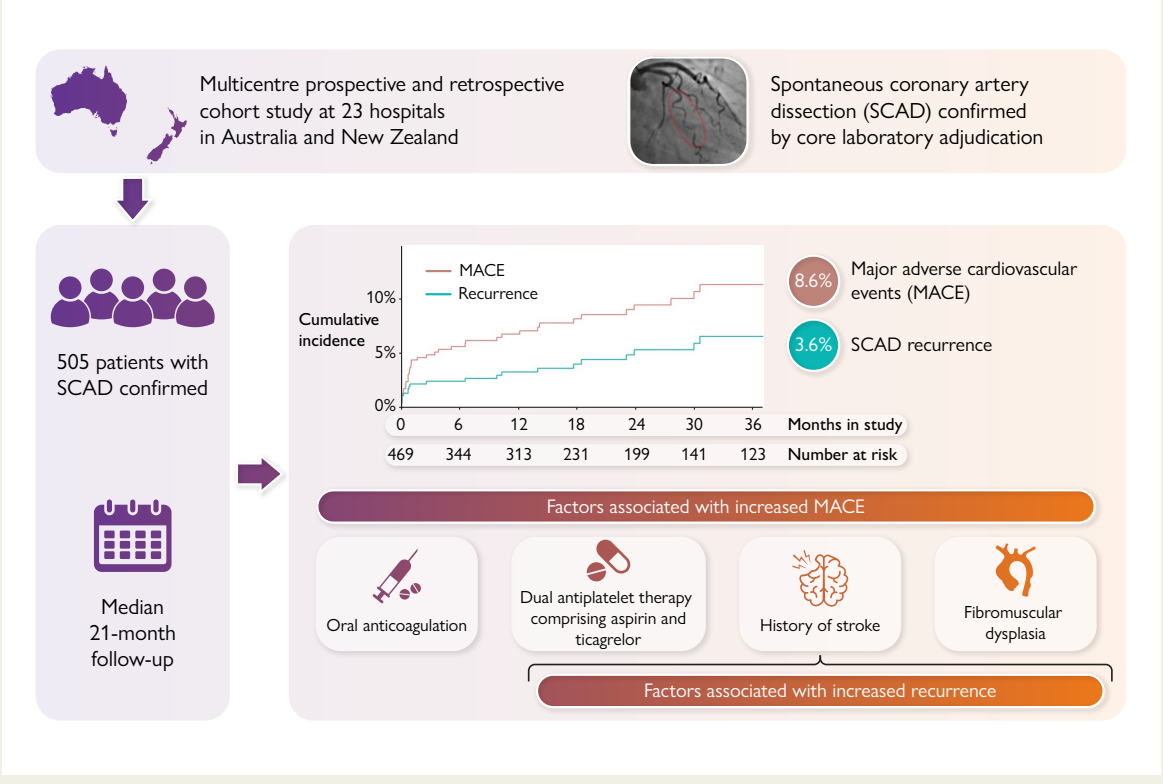
What are the clinical characteristics of patients with spontaneous coronary artery dissection (SCAD) and what are the factors associated with increased risk of major adverse cardiovascular events (MACE) and SCAD recurrence?

Key Finding

In this multicentre study in 505 patients with SCAD, MACE occurred in 8.6% and recurrence in 3.6% after 21-month follow-up. Dual antiplatelet therapy involving ticagrelor (but not clopidogrel), fibromuscular dysplasia (FMD), and history of stroke were associated with higher risk of MACE and SCAD recurrence. In addition, oral anticoagulation was associated with increased MACE.

Take Home Message

SCAD is associated with significant risk of MACE. Caution is needed with anticoagulation or dual antiplatelet therapy combining aspirin and ticagrelor. FMD screening should be performed for all patients with SCAD given its important prognostic association.



Findings from the Australian-New Zealand Spontaneous Coronary Artery Dissection Registry study.

Keywords Spontaneous coronary artery dissection • Major adverse cardiovascular event • Recurrence • Acute coronary syndrome • Myocardial infarction • Ticagrelor • Anticoagulation • Fibromuscular dysplasia

Introduction

Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of acute coronary syndrome (ACS),[1–3] accounting for up to one-third of ACS among women under age 50 and up to one-half of myocardial infarction (MI) in pregnant women.[4–7] While recognition of SCAD has increased,[8] understanding of the condition remains incomplete, with a paucity of prospective data and no randomized controlled trials to guide treatment. Despite differing pathophysiology, many patients with SCAD are treated similarly to those with atherosclerotic ACS, receiving dual antiplatelet therapy (DAPT) and statins. Of concern, recent observational data found that DAPT was associated with higher major adverse cardiovascular events (MACEs) than the use of single antiplatelet therapy (SAPT).[9] Other cohort studies have identified an association between beta-blocker use and lower SCAD recurrence.[10,11] There is a lack of research assessing the utility of screening for fibromuscular dysplasia (FMD) and its association with recurrent events in SCAD survivors. Moreover, referral to cardiac rehabilitation is recommended for all post-ACS patients, yet the rates of referral or attendance of people with SCAD remain poorly described.[12]

The Australian-New Zealand SCAD (ANZ-SCAD) Registry was established in 2021 as a multicentre, prospective, and retrospective cohort study, recruiting patients from diverse geographic sites across the two countries.[13] This is the first report from the ANZ-SCAD Registry and aims to describe demographic features and clinical presentation of people with SCAD and explore the predictors of MACE and recurrent SCAD.

Methods

Study design

The ANZ-SCAD Registry is an observational, multicentre, prospective, and retrospective cohort study recruiting patients with SCAD from 23 hospital sites in Australia and New Zealand. The study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12621000824864). Ethics approval was granted by the Western Sydney Local Health District Human Research Ethics Committee (2021/ETH00040) for the Australian sites and by the Southern Health and Disability Ethics Committee (2021 FULL 11045) for the New Zealand sites. Prospectively recruited patients gave their informed consent, while a waiver of consent was obtained for retrospectively recruited patients in accordance with the Australian National Statement on Ethical Conduct in Human Research.

Study population

Patients aged 18 years or older with a diagnosis of ACS secondary to SCAD (non-atherosclerotic and non-iatrogenic) made by invasive coronary angiography were eligible for inclusion. There were two ways of recruiting patients to the study: prospective and retrospective. In the prospective group, patients were approached at the time of their hospital admission for SCAD (or shortly after discharge) to provide their informed consent. Data were obtained from patient-completed questionnaires, medical records, and clinical follow-up for up to 5 years. In the retrospective group, each recruiting site identified historical patients with SCAD diagnosed from 2010 to 2024 with data obtained from medical records. As there was no International Classification of Diseases (ICD-10) code for SCAD, historical cases were screened by firstly searching for the term 'spontaneous coronary artery dissection' or 'coronary artery dissection' or 'dissection' in discharge summaries using electronic medical record system to maximize the chance of detecting patients with SCAD. Then, the discharge summaries were manually reviewed by study co-ordinators to identify patients with a diagnosis of SCAD.

Core laboratory review of invasive coronary angiography

Only patients with confirmed SCAD after independent core laboratory review of the invasive coronary angiography were included. Anonymized invasive coronary angiography images, as well as any repeat coronary angiography or additional imaging [e.g. intravascular imaging and/or computed tomography coronary angiography (CTCA)], were uploaded by the participating sites to CloudStor, a secure online image database hosted by the University of Sydney. Initial screening and categorization were performed by the co-ordinating centre (Westmead Applied Research Centre of the University of Sydney) by two experienced cardiologists blinded to clinical data. Core laboratory adjudication was performed by a committee consisting of five experienced interventional cardiologists with majority consensus to achieve a conclusion (S.Z., P.J.P., S.B., J.C., and S.M.).

Spontaneous coronary artery dissection was angiographically classified according to the system developed by Saw[14] and Al-Hussaini and Adlam.[15] Type 1 SCAD was defined as visible contrast in both the true and false lumens. Type 2 SCAD was a long stenosis (>20 mm) with appearance of an intramural haematoma compressing the true lumen. Type 2 SCAD was further classified into 2A (the haematoma did not extend to the tip of the vessel) and 2B (the haematoma extended to the tip of the vessel). Type 3 was characterized by a focal short stenosis (<20 mm) due to an intramural haematoma, while Type 4 SCAD was a total occlusion of the vessel. For the purpose of distinguishing Type 3 and 4 SCAD from atherosclerotic disease, the diagnosis of SCAD required other typical angiographic characteristics (e.g. Type 1 or 2 SCAD in other vessels in the case of multivessel SCAD), resolution/healing of SCAD on follow-up angiography in keeping with SCAD's natural history, or the presence of intramural haematoma on intravascular imaging. Additional coronary angiography data obtained from the core laboratory review included time of angiography, presence/degree of atherosclerosis, site and length of SCAD, revascularization with percutaneous coronary intervention (PCI) and its associated success rate and complications, and degree of tortuosity (mild, moderate, or severe) based on the system proposed by Eleid *et al.*[16]

Data collection, data management, and follow-up

Study data were collected and managed using REDCap, a secure, web-based software platform hosted by the University of Sydney. Data were extracted from the medical records for all recruited patients including baseline and presentation characteristics, past medical history (including history of mental health disorders), in-hospital investigations, management, and outcomes. For the prospective arm, patients completed electronic questionnaires at 30 days, 1 year, and then yearly for up to 5 years. Data collected included cardiovascular risk factors, clinical precipitants, discharge medications, use of FMD screening and presence of FMD, referral and attendance at cardiac rehabilitation, clinical outcomes, angina burden, and quality of life. Telephone follow-up was performed for patients who did not respond, or who were unable to be followed electronically, with the use of interpreters as required. If a patient could not be contacted on multiple occasions, study co-ordinators would contact the patient's doctor to confirm if the patient was still alive or last time known to be alive. In the retrospective arm, last date of contact and outcomes were taken from the available medical records (hospital records, cardiologist's rooms, and general practitioner follow-up) at the time of recruitment. A dedicated SCAD research team at the Westmead Applied Research Centre performed quality control, generated queries for missing data, and undertook source verification of coronary angiography and other imaging reports.

Outcomes

The primary endpoint was the occurrence of a MACE, defined as death from any cause, non-fatal MI (either secondary to SCAD or non-SCAD related MI), non-fatal stroke, heart failure, or coronary revascularization. Secondary endpoints included each component of the primary endpoint,

as well as SCAD recurrence. Spontaneous coronary artery dissection recurrence was defined as *de novo* recurrent spontaneous dissection with new ACS symptoms and cardiac biomarker elevation, not involving extension of the index SCAD. In the case of recurrent SCAD or repeat hospital admission for ACS, follow-up coronary angiography was obtained and reviewed by the core laboratory to ascertain the site of new SCAD and confirm healing of the initial SCAD. In prospective patients, additional patient-reported outcome measures included quality of life, as measured by the EQ-5D™ questionnaire, and anginal symptoms (as measured by the Seattle Angina Questionnaire).[17–19]

Statistical analysis

Analysis was performed on the full study cohort, with pre-specified statistical analysis plan. The mean and standard deviation were calculated for normally distributed continuous variables, while median and inter-quartile ranges (IQRs) were obtained for non-normally distributed variables. Counts and proportions were used to describe categorical variables. Univariable and multivariable Cox proportional hazard models were used to evaluate the association between pre-specified clinical variables and the occurrence of MACE. For each of the parameters, a hazard ratio (HR) with 95% confidence interval (CI) and *P*-value were calculated. Pre-specified variables were selected based on past literature as well as those deemed clinically relevant, including age, sex, number of pregnancies, past medical history (including typical cardiovascular disease risk factors and mental health conditions), the presence of FMD, ST-elevation MI (STEMI) on presentation, proximal location of SCAD, impaired coronary flow on angiography, multivessel SCAD, angiographic Subtype 2A, treatment strategies (conservative vs. invasive), and medications on discharge.[9,10,20–26] The method of recruitment (prospective vs. retrospective) was not included as a variable for outcome analysis as this was considered to be inextricably associated with multiple confounders, including time of event and availability of patient's data. All parameters with a *P*-value <.1 in the univariable analysis were included in multivariable analysis. A backward stepwise selection process was used to obtain the final model. During this process, multivariable Cox proportional hazard model was initially performed on all included variables. Then, the variable with the highest *P*-value was sequentially eliminated until the *P*-values of all the remaining variables were statistically significant. Statistical analysis was performed with R-Studio statistical software. The following R packages were used: tidyverse, skimr, rstatix, anytime, lubridate, gtsummary, survival, ggsurffit, tidycmprsk, rms, survminer, ggplot2, and epitools. A two-tailed *P*-value of <.05 was considered statistically significant. Similar analysis was performed in a pre-specified subgroup of patients who were managed conservatively, defined as patients who did not have any attempt on coronary intervention (e.g. stenting, wiring, or balloon angioplasty).

Results

Baseline characteristics

A total of 586 patients were screened for inclusion on the basis of a clinical diagnosis of SCAD made by the recruiting site, with invasive coronary angiography imaging available for review in the core laboratory. From these patients, 81 (15.3%) were excluded following core laboratory adjudication, due to either a diagnosis of SCAD deemed unlikely based on the available imaging or a SCAD diagnosis unable to be definitively confirmed (e.g. due to lack of intravascular imaging in the case of Type 3 SCAD, lack of follow-up angiography to demonstrate healing, or a large burden of atherosclerosis in non-culprit vessels that made the diagnosis less likely). Of the 505 included patients, 150 (29.7%) were prospectively recruited and 355 (70.3%) retrospectively recruited. Index hospital admission was between January 2010 and May 2024.

Baseline characteristics are shown in *Table 1*, with prospective and retrospective cohorts similar in age, sex, and body mass index but with differences in ethnicity (of note, ethnicity was self-reported by prospective participants, while data on ethnicity were obtained from available medical records in retrospective patients). The mean age at time of SCAD diagnosis was 52.2 ± 10.6 years, 88.7% (*n* = 448) were female, and 78.6% (*n* = 376) were Caucasian, 4.4% (*n* = 21) Māori, 3.3% (*n* = 16) East Asian, 1.7% (*n* = 8) South Asian, and 9.6% (*n* = 46) other ethnicities. The median follow-up time was 21 months (IQR 8–39 months). At least one standard cardiovascular risk factor was present in 60.6% (*n* = 306) of patients, with previously diagnosed hypertension the most common (*n* = 141, 27.9%), followed by family history of premature coronary artery disease (*n* = 116, 23.0%), dyslipidaemia (*n* = 108, 21.4%), current smoker (*n* = 87, 17.7%), and diabetes mellitus (*n* = 11, 2.2%). All patients presented with an ACS as per inclusion criteria, with 64.7% (*n* = 326) non-STEMI (NSTEMI) and 33.1% (*n* = 167) STEMI. Among those with STEMI, fibrinolysis was given in 36 patients (21.6%). A potential trigger of SCAD was identified in 46.9% (*n* = 237) of cases with emotional stress (*n* = 167, 33.1% of total patients) and physical stress (*n* = 73, 14.5% of total patients) being the most common precipitants. A history of a mental health disorder occurred in 18.8% (*n* = 95), including depression (*n* = 67, 13.3%) and anxiety (*n* = 5 3, 10.5%). The number of pregnancy and number of live births were only available for prospectively recruited patients. Out of 128 prospectively recruited females, 14 had never been pregnant, 57 had had one to two pregnancies, and 52 had three or more pregnancies.

Core laboratory coronary angiography findings are summarized in *Table 2* with similar anatomical features between retrospective and prospectively recruited participants. The left anterior descending artery was the vessel most commonly affected by SCAD (*n* = 254, 51.5%), followed by the left circumflex artery (*n* = 136, 26.9%) and right coronary artery (*n* = 114, 22.6%). Most SCAD cases were classified as Type 2 (*n* = 421, 83.4%) with multivessel SCAD occurring in 9.5% (*n* = 48) of the cohort. Intravascular imaging was performed in 3.4% (*n* = 17) of patients, 9.3% (*n* = 47) also had CTCA and 11.3% (*n* = 57) had follow-up invasive coronary angiography. The majority (*n* = 447, 88.5%) of patients were managed conservatively. A total of 10.7% (*n* = 54) of patients underwent attempted or successful PCI, consisting of stenting (*n* = 29, 53.7%), balloon angioplasty alone (*n* = 11, 20.4%), or wiring only (*n* = 14, 25.9%). The procedural complication rate was 33.3% (*n* = 18) in patients with PCI, compared with 0.7% (*n* = 3) in patients undergoing angiography but otherwise managed conservatively. Extension of culprit SCAD was only observed in five patients, four of whom were managed conservatively.

Discharge medications are shown in *Table 3*, with 95.7% (*n* = 483) of patients prescribed at least one antiplatelet agent and 64.0% (*n* = 323) receiving DAPT. The proportion of patients receiving DAPT comprising aspirin plus clopidogrel (*n* = 159, 31.5%) was similar to the proportion of patients receiving aspirin plus ticagrelor (*n* = 163, 32.3%). Prospective patients were less likely to be discharged on DAPT than retrospective patients. A total of 4.4% (*n* = 22) of patients were discharged on an oral anticoagulant, either alone (*n* = 8, 1.6%) or in combination with a single antiplatelet (*n* = 14, 2.8%). Among those discharged on anticoagulation, 15/22 were on anticoagulation prior to admission, one had a mechanical heart valve, and two had a history of atrial fibrillation; in the remainder, the reason was not reported. Beta-blockers were prescribed in 81.0% (*n* = 409) of patients and statins in 55.8% (*n* = 282). FMD screening was performed in 38.6% (*n* = 182) of patients, and, of those screened [the majority with computed tomography (CT) angiography], FMD was diagnosed in 30.2% (*n* = 55) and an extra-cardiac vascular abnormality other than FMD (e.g. vascular aneurysms) in 11.5% (*n* = 21). The majority (*n* = 126, 69.2%) of

Table 1 Baseline characteristics

Characteristic [*n* (%), unless stated otherwise]	Total (*n* = 505)	Prospective (*n* = 150)	Retrospective (*n* = 355)	*P*-value
Age, years (mean ± SD)	52.2 ± 10.6	53.2 ± 11.2	51.7 ± 10.3	.17
Female sex	448 (88.7%)	128 (85.3%)	320 (90.1%)	.13
Ethnicity				.01*
Caucasian	376 (78.6%)	127 (86.4%)	249 (75.2%)	
East Asian	16 (3.3%)	7 (4.8%)	9 (2.7%)	
South Asian	8 (1.7%)	3 (2.0%)	5 (1.5%)	
Aboriginal and Torres Strait Islander	5 (1.0%)	2 (1.3%)	3 (0.9%)	
Māori	21 (4.4%)	4 (2.7%)	17 (5.1%)	
Pacific people	6 (1.3%)	1 (.7%)	5 (1.5%)	
Other/unknown (included African, North African, and Middle Eastern countries)	46 (9.6%)	3 (2.0%)	43 (13.9%)	
Missing	27 (5.3%)	3 (2.0%)	24 (6.8%)	
Body mass index, kg/m^2 (mean ± SD)	29.1 ± 12.8	28.1 ± 6.2	29.6 ± 15.0	.16
Hypertension	141 (27.9%)	45 (30.0%)	96 (27.0%)	.50
Diabetes mellitus	11 (2.2%)	3 (2.0%)	8 (2.3%)	1.00
Dyslipidaemia	108 (21.4%)	31 (20.7%)	77 (21.7%)	.80
Family history of premature CAD	116 (23.0%)	34 (22.7%)	82 (23.1%)	.92
Previous MI	33 (6.5%)	12 (8.0%)	21 (5.9%)	.39
Previous stroke	7 (1.4%)	1 (0.7%)	6 (1.7%)	.68
Atrial fibrillation	7 (1.4%)	5 (3.3%)	2 (0.6%)	.03*
Known FMD	4 (0.8%)	2 (1.3%)	2 (0.6%)	.59
Known extra-cardiac vascular aneurysm/dissection	5 (1.0%)	1 (0.7%)	4 (1.1%)	1.00
Migraine	64 (12.7%)	26 (17.3%)	38 (10.7%)	.04*
Depression	67 (13.3%)	31 (20.7%)	36 (10.1%)	.001*
Anxiety	53 (10.5%)	21 (14.0%)	32 (9.0%)	.09
Smoking status				.16
Lifelong non-smoker	322 (65.6%)	103 (69.1%)	219 (61.7%)	
Current smoker	87 (17.7%)	19 (12.8%)	68 (19.2%)	
Ex-smoker	82 (16.7%)	27 (18.1%)	55 (15.5%)	
Missing	14 (2.8%)	1 (0.7%)	13 (3.7%)	
Hormone replacement therapy or oral contraceptive	28 (5.5%)	7 (4.7%)	19 (5.4%)	.67
Type of ACS at presentation				.15
STEMI	168 (33.1%)	54 (36.0%)	114 (32.2%)	
NSTEMI	326 (64.7%)	96 (64.0%)	230 (65.0%)	
Unstable angina	10 (2.0%)	0 (0%)	10 (2.8%)	
Missing	1 (0.2%)	0 (0%)	1 (0.3%)	
Out-of-hospital cardiac arrest at presentation	6 (1.2%)	1 (0.7%)	5 (1.4%)	1.00
Precipitant for ACS (participants can select more than one precipitant)				.20
None identified	268 (53.1%)	11 (7.3%)	257 (72.4%)	
Pregnancy or post-partum	33 (6.5%)	26 (17.3%)	7 (2.0%)	
Physical stress	73 (14.5%)	32 (21.3%)	41 (11.5%)	

Continued

Table 1 *Continued*

Characteristic [*n* (%), unless stated otherwise]	Total (*n* = 505)	Prospective (*n* = 150)	Retrospective (*n* = 355)	*P*-value
Emotional stress	167 (33.1%)	115 (76.7%)	52 (14.6%)	
Illicit drug/medication use	20 (4.0%)	13 (8.7%)	7 (2.0%)	
Left ventricular ejection fraction (in participants who underwent inpatient LVEF assessment)				.55
>50%	162 (72.0%)	50 (79.4%)	112 (69.1%)	
40%–50%	43 (19.1%)	10 (15.9%)	33 (20.4%)	
<40%	20 (8.9%)	3 (4.8%)	17 (10.5%)	

*Indicates *P* values of statistical significance.
CAD, coronary artery disease; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation MI; SD, standard deviation.

patients underwent screening for FMD either during their hospital admission or within 30 days and only one patient had FMD screening after a MACE event.

Fibromuscular dysplasia screening and referral to cardiac rehabilitation were performed significantly more frequently in prospectively recruited participants (noting that retrospective patients were recruited over the past 10 years while prospective patients were recruited from 2021 to current) (*Figure 1*).

Outcomes

The cumulated MACE was 8.6% at median follow-up of 21 months and 11.3% at 3 years (*Figure 2*). The 3-year cumulative components of each MACE were 1.6% death, 5.7% non-fatal MI, 1.6% non-fatal stroke, 1.7% target vessel revascularization, and 1.5% heart failure (Supplementary data online, *Figures 1–4*) . Five patients died in the hospital during their index SCAD, while four died on follow-up. Among those who died on follow-up, two patients died from a haemorrhagic stroke, with one confirmed to be from a complication of FMD (vertebral artery aneurysm rupture), one died from metastatic breast cancer, and one with unclear cause of death. Final multivariable Cox proportional hazard models are shown in *Table 4*, while univariable models were provided in Supplementary data online, *Table S1*. In the univariable model, history of stroke (HR 3.7, 95% CI 1.2– 12, $P = .027$), atrial fibrillation (HR 4.5, 95% CI 1.1–19, $P = .039$), use of anticoagulation on discharge (HR 2.9, 95% CI 1.3–6.9, $P = .013$), and history of depression (HR 2, 95% CI 1.1–37, $P = .024$) were associated with higher risk of MACE. In the multivariable model, the use of DAPT comprising aspirin and ticagrelor [adjusted HR (aHR) 1.8, 95% CI 1.04–3.2, $P = .037$], use of anticoagulation on discharge (aHR 3.8, 95% CI 1.6–9.3, $P = .003$), prior stroke (aHR 3.8, 95% CI 1.2–12.2, $P = .03$), and a diagnosis of FMD (aHR 2.2, 95% CI 1.05–4.5, $P = .037$) were independently associated with higher risk of MACE. As FMD and stroke may be associated with each other, additional statistical analysis using Fisher's exact test was used, to show no significant collinearity between these two variables ($P = .56$) (see Supplementary data online, *Table S3*).

In the pre-specified subgroup analysis for patients who were managed conservatively ($n = 451$), the multivariable model found similar associations: four variables were independently associated with higher risk of MACE: DAPT comprising ticagrelor (aHR 2.2, 95% CI 1.2–4.1, $P = .011$), use of oral anticoagulation on discharge (aHR 3.3, 95% CI 1.1–9.9, $P = .035$), FMD (aHR 3.0, 95% CI 1.4–6.3, $P = .005$), and atrial fibrillation (aHR 5.0, 95% CI 1.1–22.8, $P = .040$).

The accumulated rate of SCAD recurrence was 3.6% after median 21-month follow-up and 5.7% at 3 years. In univariable model (see Supplementary data online, *Table S2*), history of stroke (HR 5.3, 95% CI 1.3–22, $P = .024$), presence of FMD (HR 4.1, 95% CI 1.7–9.9, $P = .002$), and DAPT comprising aspirin and ticagrelor (HR 2.6, 95% CI 1.3–5.5, $P = .01$) were associated with higher risk of recurrence. In the final multivariable model (*Table 5*), use of DAPT comprising aspirin and ticagrelor was independently associated with higher risk of SCAD recurrence (aHR 2.6, 95% CI 2.1–5.3, $P = .01$), as were a diagnosis of FMD (aHR 3.9, 95% CI 1.5–26.5, $P = .01$) and history of stroke (aHR 6.2, 95% CI 1.8–9.5, $P = .01$). Cumulative incidence of MACE and recurrence are illustrated in *Figure 2*.

The presence of FMD together with other vascular abnormalities (not meeting FMD diagnosis) was a stronger predictor of MACE and recurrence than FMD alone (aHR 2.7, 95% CI 1.4–5.1, $P = .002$ for MACE and aHR 4.0, 95% CI 1.8–8.9, $P < .001$ for recurrence). Beta-blocker use was not an independent factor associated with MACE or SCAD recurrence.

Discussion

This research is the largest Australasian cohort study of patients with SCAD confirmed by independent core laboratory adjudication. The current study resulted in hypothesis generating, new, and clinically important findings relating to the association between adverse outcomes and the use of anticoagulation and DAPT containing ticagrelor following SCAD (*Structured Graphical Abstract*). Oral anticoagulation, although uncommon, was associated with an adjusted 3.8 times higher risk of MACE, a finding that has not been previously reported. Use of DAPT combining aspirin with ticagrelor (but not clopidogrel) was associated with an adjusted 1.8 times higher risk of MACE. The potentially harmful association of anticoagulation and DAPT with potent $P2Y_{12}$ inhibitors in people with SCAD may be related to the underlying pathology of an intramural haematoma, and this highlights the need for further study to guide the safe and effective use of antiplatelet and antithrombotic agents in these individuals.

A potentially harmful association of DAPT with adverse outcomes in people with SCAD was reported in a retrospective study of 199 patients managed conservatively in the European DISCO registry.[9] Although 36% of patients were on ticagrelor, 63% on clopidogrel, and 1% on prasugrel in that study, detailed outcomes were not provided according to the type of $P2Y_{12}$ inhibitor used, likely due to the

Table 2 Coronary angiographic findings on core laboratory adjudication

Angiographic characteristic	Total ($n = 505$)	Prospective ($n = 150$)	Retrospective ($n = 355$)	*P*-value
Coronary artery affected				.30
Left main	3 (0.6%)	1 (0.7%)	2 (0.6%)	
LAD/diagonal/septal	254 (51.5%)	60 (40%)	194 (54.6%)	
LCx/OM/L-PLV/L-PDA	136 (26.9%)	53 (35.3%)	83 (23.4%)	
Ramus intermediate	18 (3.6%)	4 (2.7%)	14 (3.9%)	
RCA/R-PDA/R-PLV	114 (22.6%)	21 (14.0%)	93 (26.2%)	
Type of SCAD				.26
Type 1	46 (9.1%)	8 (5.3%)	38 (10.7%)	
Type 2A	222 (44.0%)	69 (56.0%)	153 (43.1%)	
Type 2B	199 (39.4%)	60 (40.0%)	139 (39.2%)	
Type 3	19 (3.8%)	8 (5.3%)	11 (3.1%)	
Type 4	19 (3.8%)	4 (2.7%)	15 (4.2%)	
Location of SCAD in vessel				.30
Proximal	58 (11.5%)	10 (6.7%)	48 (13.5%)	
Mid	197 (39.0%)	59 (39.3%)	138 (38.9%)	
Distal	250 (49.5%)	81 (54.0%)	169 (47.6%)	
Multivessel SCAD	48 (9.5%)	12 (8.0%)	36 (10.1%)	.61
Mild atherosclerosis present	86 (17.0%)	28 (18.7%)	58 (16.3%)	.55
Atherosclerosis >50% stenosis	8 (1.6%)	3 (2.0%)	5 (1.4%)	.71
Intravascular imaging (OCT or IVUS) to culprit vessel	17 (3.4%)	6 (4.0%)	11 (3.1%)	.60
TIMI flow				.04*
TIMI 0 or 1	111 (22.0%)	27 (18.0%)	84 (23.6%)	
TIMI 2	145 (28.7%)	35 (23.3%)	110 (31.0%)	
TIMI 3	249 (49.3%)	88 (58.7%)	161 (45.4%)	
Conservatively managed	447 (88.5%)	132 (88%)	315 (88.7%)	.76
PCI performed, comprising	54 (10.7%)	17 (11.3%)	37 (10.4%)	.77
Wiring only	14 (2.8%)	5 (3.3%)	9 (2.5%)	
Balloon angioplasty without stenting	11 (2.2%)	3 (2.0%)	8 (2.3%)	
Stenting	29 (5.7%)	8 (5.3%)	21 (5.9%)	
PCI complications (percentage of those treated with PCI)	18 (33.3%)	5 (29.4%)	13 (35.1%)	.76
Slow flow/no reflow	6 (11.1%)	1 (5.9%)	5 (13.5%)	
Dissection propagation	12 (22.2%)	4 (23.5%)	8 (21.6%)	
Iatrogenic dissection	2 (3.7%)	0 (0%)	2 (5.4%)	
Coronary artery perforation	2 (3.7%)	1 (5.9%)	1 (2.7%)	

*Indicates *P* values of statistical significance.
Data are reported as *n* (%).
IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCx, left circumflex artery; OCT, optical coherence tomography; OM, obtuse marginal artery; PDA, posterior descending artery; PLV, posterior left ventricular artery; RCA, right coronary artery; TIMI, thrombolysis in MI.

lower sample size. Similarly, a recent study of 389 patients in the Spanish Registry on SCAD found that use of DAPT on discharge was an independent risk factor for MACE.[27] In the current study, there were similar numbers of patients treated with DAPT who were either on ticagrelor or clopidogrel, noting that prasugrel was not available in Australia or publicly funded in New Zealand during the recruitment period. It is well established in patients with atherothrombotic ACS that more potent $P2Y_{12}$ inhibitors are associated with reduced

Table 3 Discharge medications, fibromuscular dysplasia screening, and cardiac rehabilitation

Characteristic, no. (%)	Total ($n = 505$)	Prospective ($n = 150$)	Retrospective ($n = 355$)	*P*-value
Discharge medications				
SAPT	160 (31.7%)	56 (37.3%)	104 (29.3%)	.07
Aspirin	138 (27.3%)	50 (33.3%)	88 (24.8%)	
Clopidogrel	20 (4.0%)	6 (4.0%)	14 (3.9%)	
Ticagrelor	2 (.4%)	0 (0%)	2 (.6%)	
DAPT	323 (64.0%)	84 (56.0%)	239 (67.3%)	.016*
Aspirin + clopidogrel	159 (31.5%)	42 (28.0%)	117 (33.0%)	
Aspirin + ticagrelor	163 (32.3%)	42 (28.0%)	121 (34.1%)	
Oral anticoagulation	22 (4.4%)	12 (8.0%)	10 (2.8%)	.02*
Statin	282 (55.8%)	81 (54.0%)	201 (56.6%)	.59
ACE-I/ARB	208 (41.2%)	60 (40.0%)	148 (41.7%)	.72
Beta-blocker	409 (81.0%)	127 (84.7%)	282 (79.4%)	.17
Calcium channel blocker	48 (9.5%)	16 (10.7%)	32 (9.0%)	.17
Long-acting nitrate	40 (7.9%)	8 (5.3%)	32 (9.0%)	.16
Diuretic	24 (4.8%)	8 (5.3%)	16 (4.5%)	.65
Screened for FMD	182 (38.6%)	72 (53.7%)	110 (31.0%)	<.001*
In patients screened				
FMD diagnosed	55 (30.2%)	22 (30.6%)	33 (30.0%)	.94
Other extra-cardiac vascular abnormalities	21 (11.5%)	9 (12.5%)	12 (10.9%)	.82
Cardiac rehabilitation referral	384 (76.0%)	139 (92.7%)	245 (69.0%)	<.001*

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

ischaemic events, at the expense of higher risk of bleeding, compared with clopidogrel.[28] Given that the underlying pathology in SCAD is usually an intramural haematoma, anticoagulation and/or more potent $P2Y_{12}$ inhibition may be harmful. The finding that ticagrelor in combination with aspirin was also independently associated with a higher risk of SCAD recurrence suggests that the higher MACE was driven in part by higher SCAD recurrence. The data add to previous work showing higher MACE with DAPT in people with SCAD but suggest the harmful effect is driven by more potent $P2Y_{12}$ inhibitors. It should be noted that patients who received more potent $P2Y_{12}$ inhibitors, such as ticagrelor, over clopidogrel, may have had other high risk anatomical or clinical features, which were unadjusted for in the current models. In the current study, which involved 23 sites across Australia and New Zealand, SAPT, DAPT comprising ticagrelor, and DAPT comprising clopidogrel were used in roughly the same proportion of patients (about a third for each), and this was likely reflective of the heterogeneity in clinical practice for treatment of patients with SCAD.

Fibromuscular dysplasia was previously found to be an independent risk factor for MACE on follow-up and recurrence in other observational studies, and this was again demonstrated in the current study.[23,29] While previous work reported the increased risk with regard to FMD, we found that the presence of FMD, as well as other extra-coronary vascular abnormalities, was a strong predictor for SCAD recurrence and MACE. The findings emphasize the importance of FMD screening for all people with SCAD, to enable prognostication, consistent with current guidelines.[1–3] Despite this recommendation, current practice of FMD screening in patients with SCAD varies significantly across the world.[12] In this study, only ~40% of patients with SCAD in Australia and New Zealand underwent screening for FMD, which appears low compared with other high-income countries.[12,30] Low levels of awareness among clinicians on the need for screening could contribute to this low rate of screening observed or a hesitancy due to radiation or contrast load associated with CT angiography in a cohort that is predominantly younger women. The rate of FMD screening among prospectively recruited patients (53.7%) was significantly higher than among the retrospectively recruited ones (31.0%), suggesting a trend of increased adoption of screening among clinicians in recent times. A subgroup analysis on the group of patients who were screened for FMD ($n = 182$) was not performed, due to the relatively small sample size, which would limit the power of such analysis.

In this study, of those patients who did receive screening, a significant proportion (42%) was found to have FMD or another significant vascular abnormalities. The detection of extra-coronary FMD and other vascular abnormalities may require frequent surveillance and, in some cases, intervention, as outlined in a recent consensus document by the Society for Vascular Medicine and the European Society for Hypertension.[31] In addition, while FMD is known to be a risk factor for stroke and people with FMD may be at higher risk for intracranial vascular abnormalities, the multivariable model found that both FMD and past stroke were independent predictors of adverse outcomes.

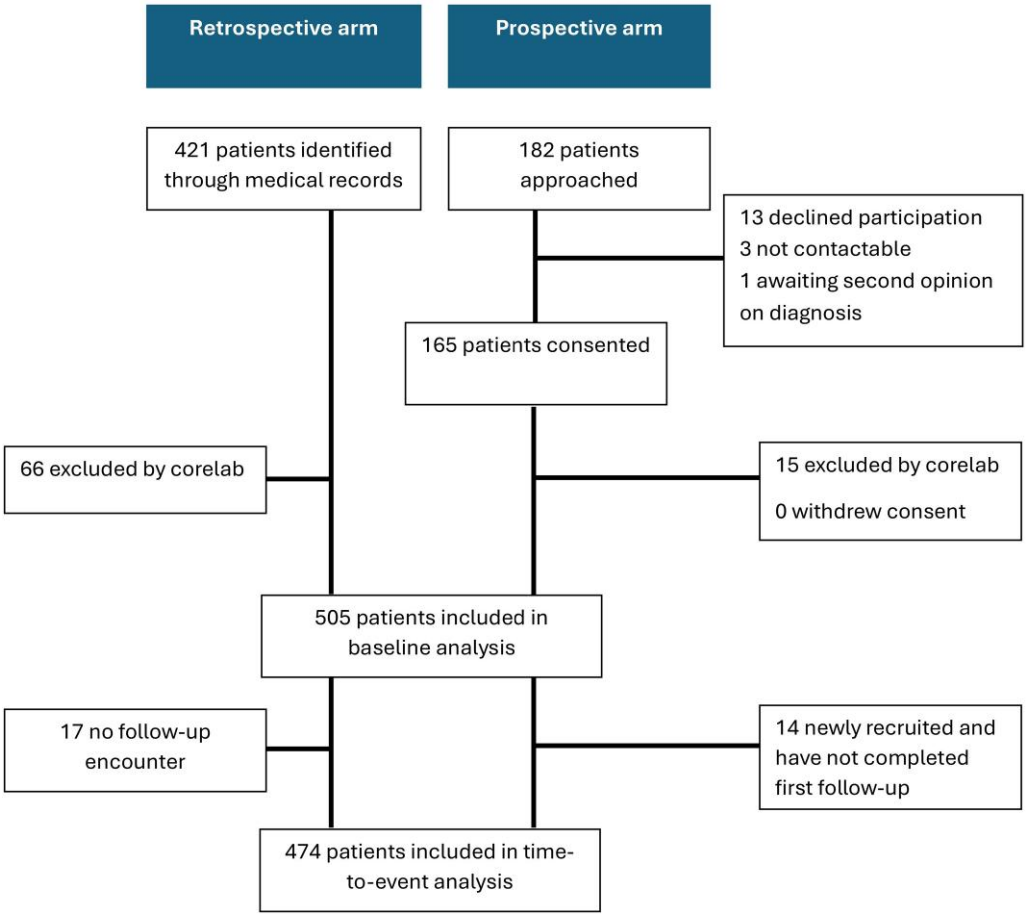


Figure 1 Flow chart of the study

In this study, the incidence of MACE of 8.6% at 21 month follow-up was consistent with other recent reports in the literature and comparable with the rate of MACE following atherosclerotic ACS.[23,32–34] These findings add to the growing body of literature demonstrating that SCAD is far from a benign condition, and it is imperative that further studies are performed to identify optimal treatment of these patients. The rate of recurrence at 3 years in this registry was higher than in the Canadian SCAD Registry (5.3% vs. 2.3%).[23] This is likely due to the lower number of patients reaching 3 year follow-up (119 of 474 vs. 726 of 750), thus having a wider CI. As this registry is still ongoing, more complete follow-up data will be available in the future. In contrast to previous studies, we did not find that beta-blocker use was associated with lower SCAD recurrence.[10,11,35] It is possible that this is a reflection of higher rates of beta-blocker use in this cohort (81%), driven by past work showing a benefit, or that different beta-blockers have not the same degree of efficacy. Given that beta-blockers are often poorly tolerated in the cohort of younger women with SCAD, a randomized controlled trial of beta-blocker use (the ongoing BA-SCAD trial) is widely anticipated.[36] Depression was found to be associated with higher risk of MACE in a previous study.[37] In this study, a history of depression was associated with higher MACE on univariable analysis but not on multivariable analysis. The proportion of people with mental health illness in this registry was relatively low compared with prior studies.[38–43] Similar to previous studies, this registry demonstrated similar MACE outcomes between invasive and conservative care for patients with SCAD.[20,44,45] This is despite a significantly higher risk of procedure-associated complications in the invasively managed group (33.3% vs 0.7%). In patients with SCAD, coronary intervention is sometimes necessary, and extreme care should be taken to minimize procedurally related complications.

The demographic characteristics of patients with SCAD in the current study have similarities to other large SCAD cohort studies, with high percentages (85%–90%) of female patients and an average age of around 50 years. Caucasian people appear to be over-represented in SCAD registries, despite recruitment in multiethnic countries like the USA or Canada, where they accounted for ~90% despite making up ~70% of the general population.[30,46–48] We aimed to recruit patients with SCAD from diverse geographic sites around Australia and New Zealand and found that while 78.6% of patients identify as Caucasian/European, there was still a high proportion of a diverse range of ethnic backgrounds. While there may be a higher level of susceptibility to SCAD among Caucasian/European individuals, SCAD clearly also affects people from other ethnic backgrounds. To our knowledge, this study was the first large-scale study to report data for Indigenous peoples in Australia and New Zealand and the Pasifika people. Only 1.2% of this cohort presented with an out-of-hospital cardiac arrest, which is low compared with 5.3% reported in the DISCO Registry.[49] The number of out-of-hospital cardiac arrest in this registry might be an under-estimation as some patients might have died before a diagnosis was made.

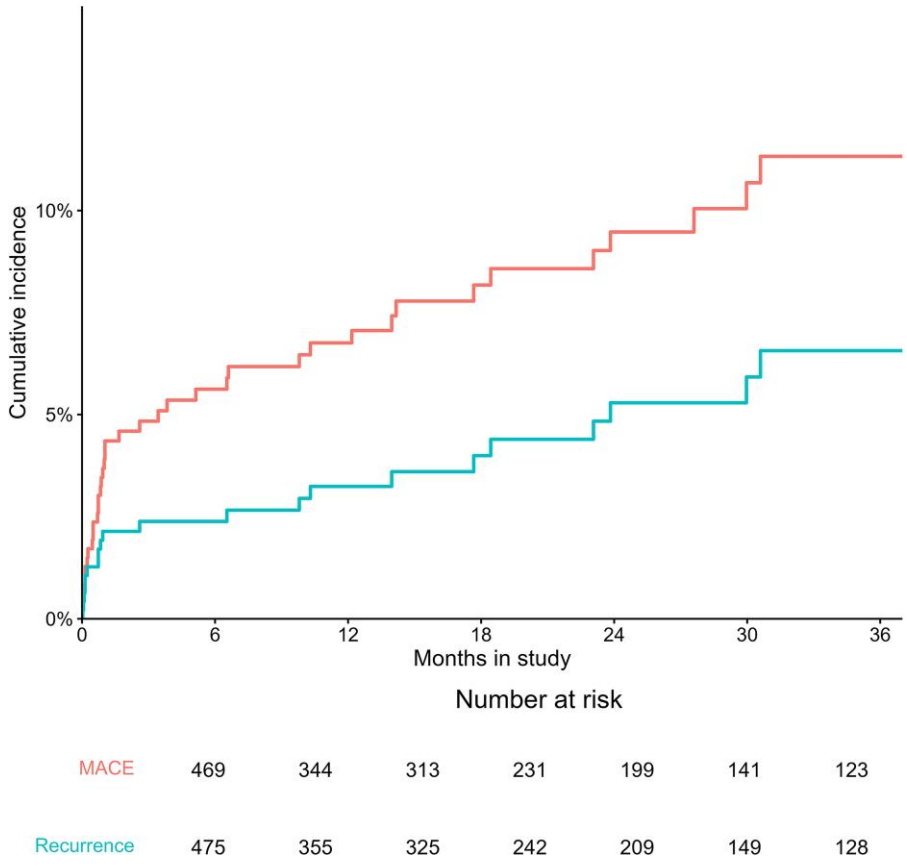


Figure 2 Cumulative incidence of major adverse cardiovascular events and recurrence in people with spontaneous coronary artery dissection. Major adverse cardiovascular event, all-cause death, non-fatal myocardial infarction, non-fatal stroke, heart failure, or target vessel revascularization; Recurrence, *de novo* recurrent spontaneous coronary artery dissection with new acute coronary syndrome symptoms and cardiac biomarker elevation, not involving extension of the index spontaneous coronary artery dissection

Table 4 Final multivariable model of determinants of major adverse cardiovascular events

Variable	Univariate HR (95% CI)	aHR (95% CI)	*P*-value
Oral anticoagulation	2.9 (1.3–6.9)	3.8 (1.6–9.3)	.003*
Aspirin + ticagrelor	1.6 (0.94–2.8)	1.8 (1.04–3.2)	.037*
FMD	2.1 (1–4.3)	2.2 (1.05–4.5)	.037*
Previous stroke	3.7 (1.2–12)	3.8 (1.2–12.2)	.03*

*P-values of statistical significance.

Table 5 Final multivariable model of determinants of spontaneous coronary artery dissection recurrence

Variable	Univariate HR (95% CI)	aHR (95% CI)	*P*-value
Aspirin + ticagrelor	2.6 (1.3–5.5)	2.6 (2.1–5.3)	.01*
FMD	4.1 (1.7–9.9)	3.9 (1.5–26.5)	.01*
Previous stroke	5.3 (1.3–22)	6.2 (1.8–9.5)	.01*

*P-values of statistical significance.

Limitations

This study was limited by its observational nature and a proportion of the data being retrospectively collected. Due to the long period of recruitment (over 14 years), time-related changes to the overall diagnosis, treatment, and outcomes of patients were potential confounders. While multivariable models were used to assess for independent predictors, we cannot adjust for unknown or unmeasured confounders. The majority (15/22) of patients who were discharged on oral anticoagulation had been on this prior to admission. For many of these patients, the reason for anticoagulation use at baseline was not available. While oral anticoagulation remained an independent predictor of MACE after adjustment for known comorbidities, including atrial fibrillation, there may be unmeasured confounders that account for the worse outcomes observed in these patients. Although statistically significant associations were found between past stroke and MACE/SCAD recurrence, the number of patients with this background history was very low ($n = 7$), and therefore, any statistical analysis should be interpreted with caution due to a large CI. As the rate of FMD screening in this study was low, the number of patients with FMD was likely an under-estimation of the true number and the true association with

MACE if all patients had been screened is unknown. In addition, these findings may be confounded by the possibility that patients deemed clinically, to be at higher risk, were more likely to receive FMD screening. In the analysis, patients who were not screened for FMD were coded as 'no FMD', and this should be considered when interpreting the results. For the findings of association of DAPT and anticoagulation with MACE, the current models were based on medications prescribed on discharge, and it was unknown if patients were still on these medications when a MACE or SCAD recurrence occurred. These results are therefore hypothesis generating and should be further investigated in randomized controlled trials.

Conclusions

Spontaneous coronary artery dissection carries a substantial risk of MACE and recurrent SCAD events and thus cannot be considered a benign condition. People with SCAD have a high rate of FMD or other extra-cardiac vascular abnormalities, and, when present, these are associated with a higher risk of MACE and recurrence. Following SCAD, discharge on oral anticoagulation and treatment with DAPT comprising aspirin and the more potent $P2Y_{12}$ inhibitor, ticagrelor, were independently associated with a higher risk of MACE. These findings add to the hypothesis that SCAD may be primarily caused by intramural bleeding (the outside-in mechanism), with the harmful association of more potent antiplatelet therapy with adverse cardiovascular events requiring further study.

Acknowledgements

We would like to foremost express our gratitude to the patients with SCAD who enrolled in this study. We pay tribute to study co-ordinators and study staff involved in caring for these patients, screening, recruitment, and data entry including nurses, allied health professionals, managers, and data scientists for their work in patient screening, recruitment, and data entry.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

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

Funding

Funding support for this work included a New South Wales Cardiovascular Research Elite Post-doctoral Grant, a CSANZ-Bayer Young Investigator Research Grant, and an Abbott unrestricted research grant to our institution. Q.M.D. received a Research Centre Stipend Scholarship by the University of Sydney. P.J.P. is supported by a National Heart Foundation of Australia Level 3 Future Leader Fellowship (FLF 106656). S.Z. is supported by a Heart Foundation Fellowship (ID 102627) and a New South Wales Health Cardiovascular Research Elite Post-doctoral Grant for this work.

Ethical Approval

Ethics approval was granted by the Western Sydney Local Health District Human Research Ethics Committee (2021/ETH00040) for the Australian sites and by the Southern Health and Disability Ethics Committee (2021 FULL 11045) for the New Zealand sites.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is ACTRN12621000824864.

References

1. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, *et al.* Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation* 2018;**137**:e523–57. https://doi.org/10.1161/CIR.0000000000000564
2. Hayes SN, Tweet MS, Adlam D, Kim ESH, Gulati R, Price JE, *et al.* Spontaneous coronary artery dissection: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**76**:961–84. https://doi.org/10.1016/j.jacc.2020.05.084
3. Adlam D, Alfonso F, Maas A, Vrints C, Writing C. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD Study Group: a position paper on spontaneous coronary artery dissection. *Eur Heart J* 2018;**39**:3353–68. https://doi.org/10.1093/eurheartj/ehy080
4. Nishiguchi T, Tanaka A, Ozaki Y, Taruya A, Fukuda S, Taguchi H, *et al.* Prevalence of spontaneous coronary artery dissection in patients with acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care* 2016;**5**:263–70. https://doi.org/10.1177/2048872613504310
5. Mortensen KH, Thuesen L, Kristensen IB, Christiansen EH. Spontaneous coronary artery dissection: a Western Denmark Heart Registry study. *Catheter Cardiovasc Interv* 2009;**74**:710–7. https://doi.org/10.1002/ccd.22115
6. Daoulah A, Al-Faifi SM, Alhamid S, Youssef AA, Alshehri M, Al-Murayeh M, *et al.* Spontaneous coronary artery dissection in the gulf: G-SCAD registry. *Angiology* 2021;**72**:32–43. https://doi.org/10.1177/0003319720946974
7. Tokura M, Taguchi I, Kageyama M, Nasuno T, Nishiyama Y, Koshiji N, *et al.* Clinical features of spontaneous coronary artery dissection. *J Cardiol* 2014;**63**:119–22. https://doi.org/10.1016/j.jjcc.2013.07.001
8. Wurdinger M, Cammann VL, Ghadri JR, Templin C. Spontaneous coronary artery dissection: a rare event? *Heart Fail Clin* 2022;**18**:189–99. https://doi.org/10.1016/j.hfc.2021.07.015
9. Cerrato E, Giacobbe F, Quadri G, Macaya F, Bianco M, Mori R, *et al.* Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry. *Eur Heart J* 2021;**42**:3161–71. https://doi.org/10.1093/eurheartj/ehab372
10. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, *et al.* Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol* 2017;**70**:1148–58. https://doi.org/10.1016/j.jacc.2017.06.053
11. Chi G, Najafi H, Montazerin SM, Lee JJ. Factors associated with recurrent spontaneous coronary artery dissection: a systematic review and meta-analysis. *Coron Artery Dis* 2022;**33**:566–73. https://doi.org/10.1097/MCA.0000000000001168
12. Dang Q, Othman F, Sheahen B, Marschner S, Psaltis P, Al-Lamee RK, *et al.* Regional and temporal variations of spontaneous coronary artery dissection care according to consensus recommendations: a systematic review and meta-analysis. *Open Heart* 2023;**10**:e002379. https://doi.org/10.1136/openhrt-2023-002379
13. Kim SK, Wing-Lun E, Chandrasekhar J, Puri A, Burgess S, Ford TJ, *et al.* The Australian New Zealand Spontaneous Coronary Artery Dissection (ANZ-SCAD) registry—a multi-centre cohort study: protocol, background and significance. *Heart Lung Circ* 2022;**31**:1612–8. https://doi.org/10.1016/j.hlc.2022.08.018
14. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. *Catheter Cardiovasc Interv* 2014;**84**:1115–22. https://doi.org/10.1002/ccd.25293
15. Al-Hussaini A, Adlam D. Spontaneous coronary artery dissection. *Heart* 2017;**103**:1043–51. https://doi.org/10.1136/heartjnl-2016-310320
16. Eleid MF, Guddeti RR, Tweet MS, Lerman A, Singh M, Best PJ, *et al.* Coronary artery tortuosity in spontaneous coronary artery dissection: angiographic characteristics and clinical implications. *Circ Cardiovasc Interv* 2014;**7**:656–62. https://doi.org/10.1161/CIRCINTERVENTIONS.114.001676
17. Viney R, Norman R, King MT, Cronin P, Street DJ, Knox S, *et al.* Time trade-off derived EQ-5D weights for Australia. *Value Health* 2011;**14**:928–36. https://doi.org/10.1016/j.jval.2011.04.009
18. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol group. *Ann Med* 2001;**33**:337–43. https://doi.org/10.3109/07853890109002087
19. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. *Circ Cardiovasc Qual Outcomes* 2014;**7**:640–7. https://doi.org/10.1161/CIRCOUTCOMES.114.000967
20. Benenati S, Giacobbe F, Zingarelli A, Macaya F, Biole C, Rossi A, *et al.* Interventional versus conservative strategy in patients with spontaneous coronary artery dissections:

insights from DISCO registry. *Circ Cardiovasc Interv* 2023;**16**:e012780. https://doi.org/10.1161/CIRCINTERVENTIONS.122.012780
21. Inohara T, McAlister C, Samuel R, Starovoytov A, Grewal T, Argote Parolis J, *et al.* Differences in revascularization strategy and outcomes by clinical presentations in spontaneous coronary artery dissection. *Can J Cardiol* 2022;**38**:1935–43. https://doi.org/10.1016/j.cjca.2022.07.008
22. Bocchino PP, Franchin L, Angelini F, D'Ascenzo F, De Ferrari GM, Alfonso F. Outcomes during the first year following spontaneous coronary artery dissection: a systematic timeframe pooled analysis. *Catheter Cardiovasc Interv* 2022;**99**:472–9. https://doi.org/10.1002/ccd.30016
23. Saw J, Starovoytov A, Aymong E, Inohara T, Alfadhel M, McAlister C, *et al.* Canadian spontaneous coronary artery dissection cohort study: 3-year outcomes. *J Am Coll Cardiol* 2022;**80**:1585–97. https://doi.org/10.1016/j.jacc.2022.08.759
24. Combaret N, Liabot Q, Deiri M, Lhermusier T, Boiffard E, Filippi E, *et al.* Characteristics and prognosis of patients with fibromuscular dysplasia in a population of spontaneous coronary artery dissections (from the French Registry of Spontaneous Coronary Artery Dissections "DISCO"). *Am J Cardiol* 2022;**175**:38–43. https://doi.org/10.1016/j.amjcard.2022.04.007
25. Benenati S, Giacobbe F, Macaya F, Patti G, Musumeci G, Gonzalo N, *et al.* Impaired culprit-vessel flow affects percutaneous coronary intervention outcomes in spontaneous coronary artery dissections. *Am J Cardiol* 2024;**219**:35–7. https://doi.org/10.1016/j.amjcard.2024.03.014
26. Ma Y, Zhong X, Yin J, Lu H, Pan C, Huang D, *et al.* Treatment strategy for spontaneous coronary artery dissection based on anatomical characteristics. *Eur J Med Res* 2023;**28**:29. https://doi.org/10.1186/s40001-023-00986-y
27. Garcia-Guimaraes M, Masotti M, Sanz-Ruiz R, Macaya F, Roura G, Nogales JM, *et al.* Clinical outcomes in spontaneous coronary artery dissection. *Heart* 2022;**108**:1530–8. https://doi.org/10.1136/heartjnl-2022-320830
28. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–57. https://doi.org/10.1056/NEJMoa0904327
29. Clare R, Duan L, Phan D, Moore N, Jorgensen M, Ichiuji A, *et al.* Characteristics and clinical outcomes of patients with spontaneous coronary artery dissection. *J Am Heart Assoc* 2019;**8**:e012570. https://doi.org/10.1161/JAHA.119.012570
30. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, *et al.* Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J* 2019;**40**:1188–97. https://doi.org/10.1093/eurheartj/ehz007
31. Gornik HL, Persu A, Adlam D, Aparicio LS, Azizi M, Boulanger M, *et al.* First International Consensus on the diagnosis and management of fibromuscular dysplasia. *Vasc Med* 2019;**24**:164–89. https://doi.org/10.1177/1358863X18821816
32. Hyun K, Negrone A, Redfern J, Atkins E, Chow C, Kilian J, *et al.* Gender difference in secondary prevention of cardiovascular disease and outcomes following the survival of acute coronary syndrome. *Heart Lung Circ* 2021;**30**:121–7. https://doi.org/10.1016/j.hlc.2020.06.026
33. Ulvenstam A, Graipe A, Irewall AL, Soderstrom L, Mooe T. Incidence and predictors of cardiovascular outcomes after acute coronary syndrome in a population-based cohort study. *Sci Rep* 2023;**13**:3447. https://doi.org/10.1038/s41598-023-30597-w
34. Franke KB, Nerlekar N, Marshall H, Psaltis PJ. Systematic review and meta-analysis of the clinical characteristics and outcomes of spontanous coronary artery dissection. *Int J Cardiol* 2021;**322**:34–9. https://doi.org/10.1016/j.ijcard.2020.08.076
35. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, *et al.* Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation* 2012;**126**:579–88. https://doi.org/10.1161/CIRCULATIONAHA.112.105718
36. Alfonso F, de la Torre Hernandez JM, Ibanez B, Sabate M, Pan M, Gulati R, *et al.* Rationale and design of the BA-SCAD (Beta-blockers and Antiplatelet agents in patients with Spontaneous Coronary Artery Dissection) randomized clinical trial. *Rev Esp Cardiol (Engl Ed)* 2022;**75**:515–22. https://doi.org/10.1016/j.recesp.2021.08.002
37. Cha S, Chang WK, Lee K, Han K, Paik NJ, Kim WS. Prevalence and impact of depression and anxiety among older myocardial infarction survivors: a nationwide cohort study. *J Affect Disord* 2024;**354**:408–15. https://doi.org/10.1016/j.jad.2024.03.043
38. Dang Q, Murphy B, Graham RM, Puri A, Ford S, Marschner S, *et al.* Patients' perspective of quality-of-care and its correlation to quality-of-life following spontaneous coronary artery dissection. *Eur J Cardiovasc Nurs* 2024;**23**:400–7. https://doi.org/10.1093/eurjcn/zvad096
39. Wagers TP, Stevens CJ, Ross KV, Leon KK, Masters KS. Spontaneous coronary artery dissection (SCAD): female survivors' experiences of stress and support. *J Cardiopulm Rehabil Prev* 2018;**38**:374–9. https://doi.org/10.1097/HCR.0000000000000330
40. Neubeck L, McHale S, Ross M, MacGillivray S, Galbraith M, Hanson C. Spontaneous coronary artery dissection: a systematic review of physical and psychosocial recovery following discharge from hospital. *Eur J Cardiovasc Nurs* 2022;**21**:665–76. https://doi.org/10.1093/eurjcn/zvac009
41. Murphy BM, Rogerson MC, Hesselson S, Iismaa SE, Graham RM, Jackson AC. Psychosocial impacts of spontaneous coronary artery dissection: a qualitative study. *PLoS One* 2022;**17**:e0273978. https://doi.org/10.1371/journal.pone.0273978
42. Liang JJ, Tweet MS, Hayes SE, Gulati R, Hayes SN. Prevalence and predictors of depression and anxiety among survivors of myocardial infarction due to spontaneous coronary artery dissection. *J Cardiopulm Rehabil Prev* 2014;**34**:138–42. https://doi.org/10.1097/HCR.0000000000000030
43. Edwards KS, Vaca KC, Naderi S, Tremmel JA. Patient-reported psychological distress after spontaneous coronary artery dissection: evidence for post-traumatic stress. *J Cardiopulm Rehabil Prev* 2019;**39**:E20–3. https://doi.org/10.1097/HCR.0000000000000460
44. Bocchino PP, Angelini F, Franchin L, D'Ascenzo F, Fortuni F, De Filippo O, *et al.* Invasive versus conservative management in spontaneous coronary artery dissection: a meta-analysis and meta-regression study. *Hellenic J Cardiol* 2021;**62**:297–303. https://doi.org/10.1016/j.hjc.2021.02.013
45. Tweet MS, Eleid MF, Best PJ, Lennon RJ, Lerman A, Rihal CS, *et al.* Spontaneous coronary artery dissection: revascularization versus conservative therapy. *Circ Cardiovasc Interv* 2014;**7**:777–86. https://doi.org/10.1161/CIRCINTERVENTIONS.114.001659
46. Johnson AK, Tweet MS, Rouleau SG, Sadosty AT, Hayes SN, Raukar NP. The presentation of spontaneous coronary artery dissection in the emergency department: signs and symptoms in an unsuspecting population. *Acad Emerg Med* 2022;**29**:423–8. https://doi.org/10.1111/acem.14426
47. Statistics Canada. *Table 98-10-0324-01 Visible Minority and Population Group by Generation Status: Canada, Provinces and Territories, Census Metropolitan Areas and Census Agglomerations With Parts*. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=9810032401 (2023, date last accessed).
48. United States Census Bureau. *Quick Facts United States*. https://www.census.gov/quickfacts/fact/table/US# (01 August 2004, date last accessed).
49. Giacobbe F, Bruno F, Brero M, Macaya F, Rolfo C, Benenati S, *et al.* Spontaneous coronary artery dissection (SCAD) with cardiac arrest at presentation: a subanalysis from the DISCO registry. *Int J Cardiol* 2024;**412**:132331. https://doi.org/10.1016/j.ijcard.2024.132331