SPONTANEOUS CORONARY ARTERY DISSECTION:

DETERMINANTS OF CLINICAL OUTCOMES, QUALITY-OF-CARE, AND QUALITY-OF-LIFE

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A thesis with published works

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STATEMENT OF ORIGINALITY

This is to certify that, to the best of my knowledge, the content presented in this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Signature:

Name: Quan Minh Dang

Date: 15th November 2025

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GENERATIVE ARTIFICIAL INTELLIGENCE STATEMENT

No content produced by generative AI tools has been used in the preparation of this thesis.

ABSTRACT

Background

Spontaneous coronary artery dissection (SCAD) is an increasingly recognised cause of acute coronary syndrome (ACS), predominantly in women without traditional risk factors. As SCAD primarily affects young and middle-aged women, at a peak age for professional and child caring commitments, the potential impact on physical and mental well-being is significant, with little data on quality-of-life (QOL) in SCAD survivors. Our understanding of SCAD management remains incomplete, with no randomised controlled trial data and limited observational studies on the current quality-of-care (QOC).

Aims

The overall aim of this thesis was to assess the long-term clinical outcomes, QOL and QOC for patients with SCAD. Specific aims of this thesis included:

- To describe the clinical presentation and long-term outcomes of SCAD and factors associated with these outcomes.
- To assess contemporary QOC of patients with SCAD and to identify factors associated with adherence to consensus recommendations for care.
- To assess the QOL of patients with SCAD in the short- and long-term, and to identify factors associated with QOL.

Methods

A narrative review summarised the current understanding of SCAD. A multi-centre cohort study, the Australia-New Zealand (ANZ) SCAD Registry, assessed clinical outcomes with multivariable Cox proportional hazard models used to explore factors associated with MACE and SCAD recurrence. Logistic regression models were used

to further examine determinants of adherence to consensus recommendations. QOL in SCAD survivors was assessed using the EQ-5D-3L questionnaire. Beta-regression models were used to assess determinants of QOL. A systematic review was performed to explore QOC in patients with SCAD, with random-effect meta-analysis used to estimate QOC parameters worldwide. An online survey of Australian SCAD survivors determined patients' perspectives on QOC and its relationship to QOL.

Results

The narrative review identified four international consensus recommendations for management of SCAD, comprising treatment with at least one antiplatelet therapy, beta-blocker therapy, cardiac rehabilitation referral, and screening for fibromuscular dysplasia (FMD).

A total of 505 patients (mean age 52.2±10.6 years, 88.6% female) were recruited to the ANZ-SCAD Registry. After a median follow-up of 21 months, 8.6% and 3.6% experienced MACE and SCAD recurrence, respectively. On multi-variable analysis, oral anticoagulation (adjusted hazard ratio [aHR] 3.8, 95% confidence interval [CI] 1.6–9.3, P = 0.003), dual-antiplatelet therapy (DAPT) comprising ticagrelor and aspirin (aHR 1.8, 95%, CI 1.04–3.2, *P* = 0.037), FMD (aHR 2.2, 95% CI 1.05–4.5, P = 0.037), and history of stroke (aHR 3.8, 95% CI 1.2–12.2, *P* = 0.03) were associated with increased risk of MACE. FMD (aHR 3.9, 95% CI 1.5–26.5, P = 0.01), DAPT comprising ticagrelor and aspirin (aHR 2.6, 95% CI 2.1–5.3, P = 0.01), and history of stroke (aHR 6.2, 95% CI 1.8–9.5, P = 0.01) were associated with increased SCAD recurrence.

A systematic review and meta-analysis of 53 studies and 8456 patients with SCAD (mean age 50.1 years, 90.6% female) found that 92.1% (95% CI 89.3-94.8%) received antiplatelets, 78.0% (CI 73.5%-82.4%) received beta-blockers, 54.4% (CI 45.4%-

63.5%) were screened for FMD and 70.2% (CI 60.8%-79.5%) were referred to cardiac rehabilitation, with significant heterogeneity in practice across the world.

In the ANZ-SCAD Registry, 95.4% received antiplatelets, 80.8% received beta-blockers, 47.8% were screened for FMD, 76.0% were referred to cardiac rehabilitation, and 33.3% received all four recommendations. Overall adherence to all four consensus recommendations increased over time (adjusted odds ratio [OR] 1.19, 95%CI 1.11-1.27) and was lower with increasing age (adjusted OR 0.98, 95%CI 0.96-0.99).

In an online survey of 172 SCAD survivors (mean age 52.6±9.2 years, 95.3% female), median reported QOC 8/10 (interquartile range 7–10), with younger people (≤50 years) more likely to report that their symptoms were not treated seriously as a heart attack ($\chi 2 = 4.127$, degree of freedom = 1, $p<0.05$). There was a significant correlation between reported QOC and QOL (OR 1.13, $p<0.001$).

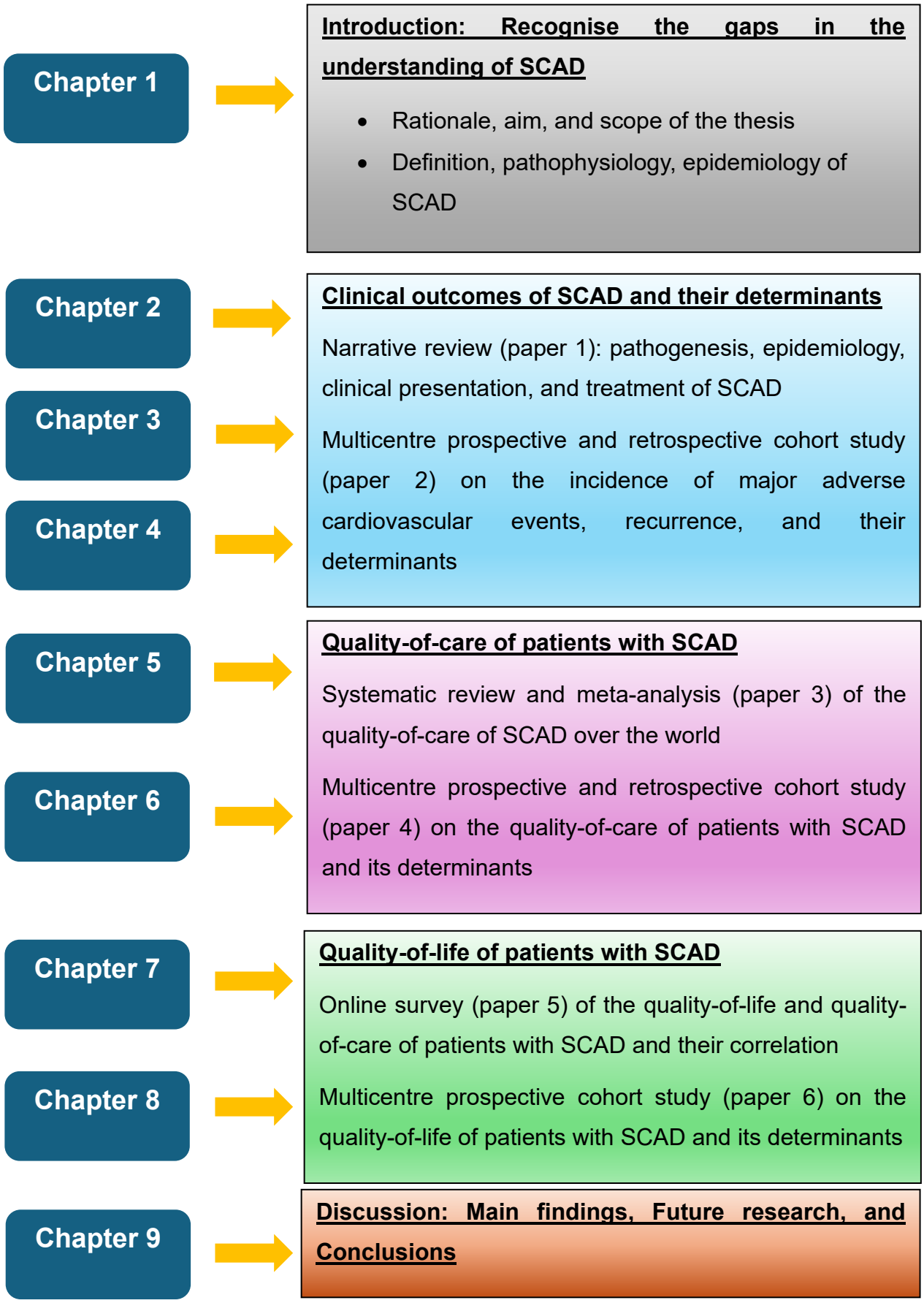
At a median of 33 days after their SCAD event, prospective patients from the ANZ-SCAD Registry (n=193, mean age 52.0±10.5, 89.1% female) reported a mean EQ-5D index summary score of 0.77±0.19, with 43.0% reporting at least moderate pain/discomfort and 57.0% at least moderate anxiety or depression. On multivariable analysis, FMD (Coefficient -0.25, p=0.005) and female sex (Coefficient -0.35, p=0.04) were independently associated with lower QOL in SCAD survivors.

Conclusion

This thesis demonstrates that SCAD was associated with ongoing risk of adverse cardiovascular outcomes, particularly in patients with fibromuscular dysplasia, prior stroke, or those treated with dual antiplatelet therapy or oral anticoagulation. Despite increasing recognition, quality-of-care remains variable worldwide, though adherence

to consensus recommendations has improved over time in Australia and New Zealand. Importantly, SCAD survivors experience significant physical and psychological burden, with quality-of-care strongly linked to quality-of-life. Collectively, these findings highlight the need for tailored management strategies, improved consistency of care, and greater patient support to optimise outcomes after SCAD.

THESIS ROADMAP



AUTHOR ATTRIBUTIONS STATEMENT

This statement is to endorse the role of Dr Quan Minh Dang in the studies that comprise the foundation of his PhD thesis. Dr Quan Minh Dang's role and responsibilities for each study are detailed in the table below:

Study	**Thesis chapter**	**Roles and Responsibilities**
Narrative review	Chapter 2 – Paper 1 (Published)	• Developed research question • Performed literature search • Drew the original illustrations • Wrote the manuscript
Cohort study of MACE and SCAD recurrence from the ANZ-SCAD Registry	Chapter 4 – Paper 2 (Published)	• Developed research question • Performed the data collection including consenting and recruiting participants • Performed the data analysis and interpretation • Drew the original illustrations • Wrote the manuscript
Systematic review and meta-analysis of quality-of-care of patients with SCAD	Chapter 5 – Paper 3 (Published)	• Developed research question • Performed the data collection • Performed the data analysis and interpretation • Wrote the manuscript
Cohort study of quality-of-care of patients with SCAD from ANZ-SCAD Registry	Chapter 6 – Paper 4 (Manuscript submitted)	• Developed research question • Performed the data collection • Performed the data analysis and interpretation • Wrote the manuscript
Online survey of quality-of-care and quality-of-life of SCAD survivors	Chapter 7 – Paper 5 (Published)	• Developed research question • Performed the data collection • Performed the data analysis and interpretation • Drew the illustration • Wrote the manuscript

Cohort study of quality-of-life of patients with SCAD	Chapter 8 – Paper 6 (Manuscript accepted for publication)	• Developed research question • Performed the data collection • Performed the data analysis and interpretation • Wrote the manuscript

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above, and the chapter specific statements, are correct.

Sincerely,

Primary PhD supervisor: Associate Professor Sarah Zaman

Signature: **Date:** 15th November 2025

Quan Minh Dang, MD **Date**: 15th November 2025

PUBLICATIONS, PRESENTATIONS, AND MEDIA ARISING FROM THIS THESIS

Publications

The following peer-reviewed publications arose from research conducted during my candidature and comprise chapters in this thesis:

1. **Dang, Q**., Burgess, S., Psaltis, P.J. et al. Spontaneous coronary artery dissection: a clinically oriented narrative review. Nature Portfolio Journal Cardiovascular Health 1, 4 (2024). https://doi.org/10.1038/s44325-024-00004-y. **Chapter 2**
2. **Quan M Dang,** Peter J Psaltis, Sonya Burgess, Jaya Chandrasekhar, Swati Mukherjee, Leonard Kritharides, Nigel Jepson, Sarah Fairley, Abdul Ihdayhid, Jamie Layland, Richard Szirt, Seif El-Jack, Aniket Puri, Esther Davis, Imran Shiekh, Ruth Arnold, Monique Watts, Jessica A Marathe, Rohan Bhagwandeen, Edwina Wing-Lun, Ravinay Bhindi, Tom Ford, Sidney Lo, Simone Marschner, Sarah Zaman, The Australian-New Zealand spontaneous coronary artery dissection cohort study: predictors of major adverse cardiovascular events and recurrence, European Heart Journal, Volume 46, Issue 21, 1 June 2025, Pages 2012–2023, https://doi.org/10.1093/eurheartj/ehaf097. **Chapter 4**
3. **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. **Chapter 5**

4. **Quan Dang**, Barbara Murphy, Robert M Graham, Aniket Puri, Sarah Ford, Simone Marschner, James J H Chong, Sarah Zaman, Patients' perspective of quality-of-care and its correlation to quality-of-life following spontaneous coronary artery dissection, European Journal of Cardiovascular Nursing, Volume 23, Issue 4, May 2024, Pages 400–407, https://doi.org/10.1093/eurjcn/zvad096. **Chapter 7**
5. **Quan M. Dang**, Mithila Zaheen, Patrick Pender, Jaya Chandrasekhar, Peter J. Psaltis, Jessica A. Marathe, et al. Health-related quality-of-life and its determinants after acute coronary syndrome caused by spontaneous coronary artery dissection. Accepted for publication by Heart, Lung and Circulation Journal. **Chapter 8**

The following manuscripts have been submitted to peer-reviewed journals, arose from research conducted during my candidature and comprise chapters in this thesis:

1. **Quan M. Dang**, Mithila Zaheen, Patrick Pender, Jaya Chandrasekhar, Peter J. Psaltis, Jessica A. Marathe, et al. Quality-of-care for Spontaneous Coronary Artery Dissection from the Australian-New Zealand SCAD Registry. Submitted May 2025- Heart, Lung and Circulation Journal (under review). **Chapter 6**

I also authored the following peer-reviewed publications during my PhD candidature:

1. Pender P, Zaheen M, **Dang QM**, Dang V, Xu J, Hollings M, et al. Spontaneous Coronary Artery Dissection: A Narrative Review of Epidemiology and Public Health Implications. Medicina. 2025;61(4):650.
2. Tait H, Kim SK, **Dang Q**, Thomas L, Kovoor P, Zaman S. Multimodal Imaging to Aid Diagnosis of Spontaneous Coronary Artery Dissection. Heart, Lung and Circulation. 2023;32(10):e73-e5.

3. Zaheen M, Pender P, **Dang QM**, Sinha E, Chong JJH, Chow CK, et al. Myocardial Infarction in the Young: Aetiology, Emerging Risk Factors, and the Role of Novel Biomarkers. Journal of Cardiovascular Development and Disease. 2025;12(4):148.
4. Munot S, Rugel EJ, Bray J, Redfern J, Yang G, Ngo L, **Dang QM**, et al. Examining training and attitudes to basic life support in multi-ethnic communities residing in New South Wales, Australia: A mixed-methods investigation. BMJ Open. 2023;13(7):e073481.

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4. Australian Government Research Training Program Scholarships (2022-2025).

Abstract and conference presentations

The following abstracts and conference presentations arose directly from research conducted during my PhD candidature:

1. [Mini Oral] **Dang Q**, Murphy B, Graham R, Puri A, Ford S, Marschner S, Chong J Zaman S. Australian Patients' Perspective of Quality of Hospital Care Following Spontaneous Coronary Artery Dissection. Presented at the 71st **Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand** (2023) in Gold Coast, Australia [Published abstract DOI: http://dx.doi.org/10.1016/j.hlc.2023.06.347].

2. [Poster] **Dang Q**, Othman F, Sheahen B, Marschner S, Psaltis P, Al Lamee R, Szirt R, Chong J, Zaman S. Australian Patients' Perspective of Quality of Hospital Care Following Spontaneous Coronary Artery Dissection. Presented at the 71st **Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand** (2023) in Gold Coast, Australia. [Published abstract DOI: http://dx.doi.org/10.1016/j.hlc.2023.06.336]
3. [Moderated ePoster] **Dang Q**, Othman F, Sheahen B, Marschner S, Psaltis P, Al Lamee R, Szirt R, Chong J, Zaman S. Australian Patients' Perspective of Quality of Hospital Care Following Spontaneous Coronary Artery Dissection. Presented at the **European Society of Cardiology Congress** (2023) in Amsterdam, the Netherlands. [Published abstract DOI: http://dx.doi.org/10.1093/eurheartj/ehad655.1394]
4. [Mini Oral] **Dang Q**, Psaltis P, Burgess S, Chandrasekhar J, Mukherjee S, Kritharides L, et al. Predictors of Major Adverse Cardiovascular Events: First Report From the Australian-New Zealand Spontaneous Coronary Artery Dissection (ANZ-SCAD) Registry. Presented at the 72nd **Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand** (2023) in Perth, Australia. [Published abstract DOI: http://dx.doi.org/10.1016/j.hlc.2024.06.521]
5. [Moderated ePoster] **Q Dang**, P Psaltis, S Burgess, J Chandrasekhar, S Mukherjee, S Fairley, J Marathe, S Zaman, Clinical characteristics and predictors of adverse cardiovascular events from the Australia-New Zealand spontaneous coronary artery dissection (ANZ-SCAD) registry. Presented at the **European Society of Cardiology Congress** (2024) in London, the United

Kingdoms. [Published abstract DOI: http://dx.doi.org/10.1093/eurheartj/ehae666.1717]

6. [Mini Oral] **Dang Q**, et al. Quality-of-care for patients with Spontaneous Coronary Artery Dissection in Australia and New Zealand. Presented at the 73rd **Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand** (2025) in Brisbane, Australia. [Abstract publication pending]
7. [Oral] **Dang Q**, et al. Adherence to consensus recommendations in the care of patients with Spontaneous Coronary Artery Dissection from the ANZ-SCAD Registry. Presented at the **European Society of Cardiology Congress** (2025) in Madrid, Spain. [Abstract publication pending]

Media Coverage and Impact of the Works

The publication that comprised chapter 4 of this thesis (Dang et al, EHJ, 2025) was featured in two news outlets and episode 11 of the ESC TV Today, a Cardiology news service from the European Society of Cardiology. The research was also featured in the Spotlight Session on Australian research presented at the European Society of Cardiology Congress 2024 and has been cited in the 2025 National Heart Foundation's Australian Acute Coronary Syndrome clinical practice guidelines (Heart, Lung Circulation) [1].

1. Brieger, D., et al., *National Heart Foundation of Australia & Cardiac Society of Australia and New Zealand: Comprehensive Australian Clinical Guideline for Diagnosing and Managing Acute Coronary Syndromes 2025*. Heart Lung Circ, 2025. **34**(4): p. 309-397.

LIST OF ABBREVIATIONS

ACS acute coronary syndrome

ACEI angiotensin converting enzyme inhibitor

ADPKD autosomal dominant polycystic kidney disease

AHA American Heart Association

ANZ Australia-New Zealand

ARB angiotensin receptor blocker

BMI body mass index

CAD coronary artery disease

CI confidence interval

CT computed tomography

CTCA computed tomography coronary angiograms

DAPT dual antiplatelet therapy

ECG electrocardiogram

ESC European Society of Cardiology

FMD fibromuscular dysplasia

GWAS genome-wide association study

IQR interquartile range

IVI intravascular imaging

IVUS intravascular ultrasound

LDS Loeys-Dietze syndrome

LVEF left ventricular ejection fraction

LVSD left ventricular systolic dysfunction

MACE major adverse cardiovascular events

MI myocardial infarction

MR magnetic resonance

NPS nail-patella syndrome

NSTEMI non-ST-elevation myocardial infarction

OCT optical coherence tomography

OR odds ratio

PCI percutaneous coronary intervention

RNA ribonucleic acid

SCAD spontaneous coronary artery dissection

SD standard deviation

STEMI ST-elevation myocardial infarction

TIA transient ischaemic attack

VAS visual analogue scale

CHAPTER 1: INTRODUCTION

Rationale, aims, and scope of this thesis

Rationale

Cardiovascular disease, an umbrella term encompassing diseases related to the blood vessels of the heart and brain, remains the leading cause of mortality and morbidity worldwide [1-3]. In Australia, despite a continuous decline since 2014, cardiovascular disease remains the number one cause of death, claiming over 26,000 lives in 2023 [4]. Spontaneous coronary artery dissection (SCAD) is an emerging cause of acute coronary syndrome (ACS), particularly in young women without traditional risk factors for atherosclerosis. It is estimated that SCAD was the cause of up to 35% of ACS [5-8] in women under 50 years of age. However, SCAD remains a poorly understood condition, with an overall prevalence of less than 5% of all ACS [9-11]. To date, there have been no randomised controlled trials to guide the care of people with SCAD. The current treatment of SCAD-related ACS is based on guidelines that have been developed for people with atherosclerotic ACS. This is far from ideal, as SCAD has a distinct pathological process that differs from atherosclerosis and, therefore, likely requires a different approach to treatment.

There are many unmet needs that require further research in SCAD. As SCAD is uncommon, large-scale prospective studies are needed to investigate the outcomes of patients with SCAD and to have the power to examine factors associated with adverse outcomes or recurrence. Significantly, few studies have determined variables that may reduce SCAD recurrence and improve major cardiovascular outcomes.

While there has been an increasing recognition of SCAD in the past decade, many patients continue to be misdiagnosed or experience delayed diagnosis [12]. Clinicians'

knowledge of SCAD, its diagnosis, and treatment, remains poor [13, 14]. This can lead to a significant burden on the patient, requiring them to source their own medical information on SCAD and advocate for their own management. In addition, a SCAD-related heart attack or acute coronary event often occurs in a young person who does not have standard risk factors for cardiovascular disease and therefore can have a profound psychological impact. The majority of affected patients are young or middle-aged women, at the prime age of often working/career and caring for dependents or planning pregnancy, and a sudden SCAD event coupled with a lack of information may lead to anxiety and poor quality-of-life. While previous studies have reported a high burden of mental health issues in SCAD survivors [13, 15-18], little research has been conducted on quality-of-life.

Aims

The overall aim of this thesis was to determine the long-term clinical outcomes, quality-of-care, and quality-of-life of patients with SCAD. Further, to identify the factors associated with major adverse cardiovascular events and SCAD recurrence.

The specific aims of this thesis were to:

1. Summarise the current understanding of the pathogenesis, aetiology, epidemiology, diagnosis, and treatment of SCAD and identify key recommendations for care (Chapter 2).
2. Establish an Australian New Zealand SCAD Registry; a multi-centre cohort study of patients with SCAD recruited at the time of their index event from Australian and New Zealand hospitals (Chapter 3).

3. Explore the incidence of long-term major adverse cardiovascular events (MACE) and the factors associated with MACE and SCAD recurrence (Chapter 4) in patients from the Australian NZ SCAD Registry
4. Explore quality-of-care measures of patients with SCAD based on the level of adherence to international consensus recommendations and explore the change in care over time (chapter 5).
5. Assess Australian SCAD survivors' perceptions of quality-of-care and its correlation with quality-of-life (chapter 6).
6. Assess adherence to the quality-of-care measures based on the international consensus recommendations in Australia and New Zealand from the ANZ-SCAD Registry (chapter 7).
7. Assess the quality-of-life of SCAD survivors, as measured by the EQ-5D-3L questionnaire, and factors associated with lower or higher quality-of-life in patients from the ANZ-NZ SCAD Registry (chapter 8).

Scope

Chapter 2 (Paper 1): A narrative review of the current literature on SCAD with a focus on clinical diagnosis and management. Published review 2024.

Chapter 3: The methodology of the ANZ-SCAD Registry, which comprised a core component of this thesis, and led to Papers 2, 4, and 6.

Chapter 4 (Paper 2): a prospective and retrospective cohort study analysing 505 patients from the ANZ-SCAD Registry. The rate of MACE and SCAD recurrence was described using cumulative incidence curves. Factors associated with worse

outcomes and increased recurrence were identified using multiple-variable Cox proportional hazard models. Published original research 2025.

Chapter 5 (Paper 3): A systematic review and meta-analysis on the quality-of-care of patients with SCAD as measured by adherence to consensus recommendations, and the change in practice over time. A total of 53 studies with 8456 patients were included. Random-effect meta-analysis was used to estimate the quality-of-care parameters. Published original research 2023.

Chapter 6 (Paper 4): A prospective and retrospective cohort study using 567 patients from the ANZ-SCAD Registry. Quality-of-care was assessed by adherence to consensus recommendations. Uni-variable and multi-variable logistic regression model was used to evaluate change in practice over time and to explore factors associated with adherence. Paper under journal review (submitted August 2025).

Chapter 7 (Paper 5): An online survey of 172 SCAD survivors in Australia who rated the quality of the care they received during their index SCAD event. Quality-of-life was assessed using the EQ-5D-3L questionnaire. Published original research 2022.

Chapter 8 (Paper 6): A prospective cohort study of 193 patients from the ANZ-SCAD Registry assessing quality-of-life using the EQ-5D-3L questionnaire. Multi-variable beta-regression and logistic-regression were used to explore determinants of EQ-5D-3L score and components. Paper under journal review (submitted August 2025).

Chapter 9: Discussion of the main findings of this thesis and areas for future research.

Definition of SCAD

Spontaneous coronary artery dissection (SCAD) is a sudden separation of the layers of the coronary artery wall that occurs spontaneously and is not related to atherosclerotic, traumatic, or iatrogenic causes. When the layers of the artery separate, blood can pool in between any of the three layers (intima, media, and adventitia), forming a haematoma and false lumen, with or without an intimal tear [19, 20]. Compression of the true lumen leads to slow blood flow through the coronary artery, resulting in acute myocardial infarction (MI), cardiac arrhythmia, and sometimes sudden cardiac death. SCAD disproportionately affects younger women. In most of the cohorts with SCAD, women comprise 80-90% of the patients [16, 21-45] and hence it has been a condition that has been well known to have a strong female predominance.

Epidemiology of SCAD

SCAD was once thought to be a rare condition [46]. The first description of SCAD was a case report published in 1931 [47]. In this case report, a 42-year-old, previously healthy woman developed acute chest pain and died suddenly after earlier symptoms of nausea and vomiting with violent retching. On autopsy, a large amount of blood was found in the pericardium with a dissecting aneurysm found in the right coronary artery, thought to be the cause of the haemopericardium. The term “spontaneous coronary artery dissection” was first used by Waksmonski in a case report published in 1978 [48]. Prior to this, it had been known as primary dissecting aneurysm of the coronary artery [49], or dissecting intramural haemorrhage of the coronary artery [50] or intramural dissecting hematoma of the coronary artery [51]. Before the year 2014,

fewer than 800 cases of SCAD were reported in the literature worldwide. However, since its increasing recognition, it has become apparent that this is not a rare condition. Consequently, SCAD has been more recently reported to be the cause of 1% to 4.8% of all acute coronary syndromes (ACS) [40, 45, 52-56] and more than 50,000 cases of SCAD have now been described through multiple registry studies [11, 21, 26, 30, 34, 38, 40-42, 57-63]. The prevalence of SCAD, in contrast to atherosclerotic coronary artery disease (CAD), decreases with increasing age [64].

SCAD has been well described to have a strong female predominance; in most cohort studies of SCAD, women made up 80-90% of the patients [8, 39, 40, 42, 58, 65, 66]. This female predominance was observed in studies worldwide, with the only exception being a cohort study in the Persian Gulf area (the G-SCAD Registry), where females comprised only 50.6% of the patients. As there was a lack of core laboratory adjudication in this study, it was possible that patients with atherosclerotic acute coronary syndrome (ACS) were also included, significantly skewing the female proportion. SCAD has been reported to be the cause of up to 35% of ACS in women under the age of 50 [5, 8, 67]. However, while SCAD is a female-predominant condition, it can occur in men. In a study of 1173 patients with SCAD, 10.5% were male [68]. Men were younger than women at the age of their SCAD event (mean age 49.4 vs 52.0, p =0.01) and were less likely to have fibromuscular dysplasia (27.8% vs 52.7%, p=0.001), depression (9.8% vs 20.2%; P = 0.005), or emotional stress (35.0% vs 59.3%; P < 0.001). Men were more likely to have isometric physical stress as a trigger, compared to women (40.2% vs 24.0%; P = 0.007). There were no differences in in-hospital events or major adverse cardiovascular events on follow-up (7.3% vs 12.7%; P = 0.106) [68].

SCAD is a common cause of myocardial infarction among pregnant women. Most pregnancy-associated SCAD occurs after delivery, mainly within the first week [69]. In a review of 150 cases of pregnancy-associated myocardial infarction, SCAD was the most common cause at 43% [70]. Pregnancy-associated SCAD made up about 5% to 17% of all SCAD cases [9, 65, 71, 72]. Compared to non-pregnant women, women with pregnancy-associated SCAD appeared to have a more severe clinical course with a higher risk of ST-elevation myocardial infarction (STEMI), involvement of the left-main or multiple coronary arteries, left ventricular systolic dysfunction, cardiogenic shock, and were more likely to require invasive intervention [69, 73-75]. Despite this more severe clinical course, there was no difference in the mortality rate [75]. In a study of 323 women, including 54 with pregnancy-associated SCAD, those with pregnancy-associated SCAD were younger and more likely to have multiple pregnancies, infertility therapies, or pre-eclampsia [69]. In a cohort study of women with SCAD, subsequent pregnancy was not associated with increased risk of SCAD recurrence [76].

Although SCAD cohorts have been reported in many countries worldwide, studies from North America and Europe have contributed the highest numbers of patients to date. In these studies, Caucasians made up the vast majority of the patients, with the proportion of Caucasians higher than that of the general population. For example, in the Canadian SCAD Registry, Caucasians made up 87.3% of the cohort, compared to 67.4% of the general population. In the Mayo Clinic SCAD Registry, Caucasian people made up 92.3% compared to 75.3% in the general population [42, 58, 77, 78]. To date, there have been no SCAD cohort studies in several countries, particularly low- and middle-income countries. While these findings suggest that Caucasian people, compared to other ethnicities, are more susceptible to SCAD, it is more likely due to

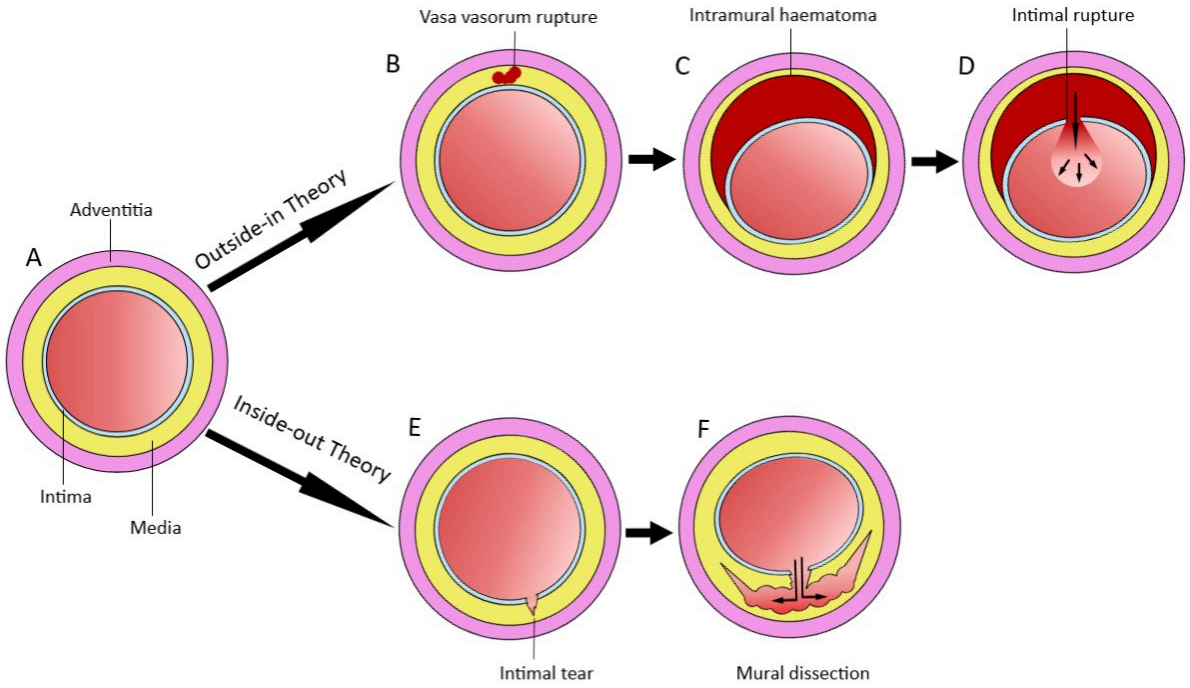
under-reporting of ethnicity as well as lack of registries in low- and middle-income countries.

Pathophysiology and Predisposing Factors for SCAD

There are two main theories about the development of SCAD: the inside-out and the outside-in [79] (figure 1). The inside-out theory postulates that a tear or break in the artery's intima is the initiating event in SCAD. Once this tear has happened, blood moves from the true lumen to dissect into the sub-intimal space, forming a false lumen. The outside-in theory, on the other hand, suggests that a haematoma is first formed in the middle layer of the blood vessel, likely secondary to the rupture of one of the vasa vasorum. This haematoma is pressurised and compresses the true lumen. If the intimal layer overlying this haematoma ruptures, then there will be a communication between the true and false lumens. The following findings support the outside-in theory: a) an intimal tear cannot always be found in SCAD [80-83], b) in non-fenestrated SCAD, features on optical coherence tomography (OCT) images were consistent with pressurisation of the false lumen [80], c) in many cases, very limited contrast can be seen in the false lumen even if there is an intimal tear, suggesting pressurisation in the false lumen with "reverse-rupture" into true lumen [80], and d) the adventitial vasa vasorum density in the normal segments of the coronary artery adjacent to the dissected segment is higher compared to control, non-SCAD subjects [84]. However, the findings that vasa vasorum density increased in patients with SCAD were obtained a median of 44 days after SCAD [84], while another study reviewing OCT images at the time of SCAD did not demonstrate a significant difference compared to non-SCAD subjects [80]. This raises the possibility that the observed increase in density was a result of healing vessels, rather than the cause or risk factor

for SCAD development [80]. For type 2 and type 3 SCAD, the outside-in theory seems to be more likely, as there is no contrast seen in the haematoma on the coronary angiogram. It is possible that for type 2 and type 3 SCAD, the outside-in mechanism is the primary one, while it may also be the mechanism in at least some cases of type 1 SCAD.

Figure 1 – The two theories on the mechanism of spontaneous coronary artery dissection development



Images are schematic representation of the cross-section of a coronary artery. A: normal coronary artery consisting of three layers; B: Rupture of vasa vasorum in the media; C: Development of intramural haematoma between the intima and the adventitia; D: Rupture of the intima, creating communication between the true and false lumens; E: Rupture of the intima as the primary event; F: dissection of the media by blood pressure from the true lumen.

Endothelial and vasomotor dysfunction have been implicated in the pathophysiology of SCAD [85, 86]. In one study, patients with SCAD were found to have poorer endothelial function (measured by reactive-hyperaemia peripheral arterial tonometry) compared to matched control individuals [87]. In most cases, the dissection in SCAD heals spontaneously (which is one of the reasons why a conservative management of SCAD is preferred). Several patients with SCAD, however, continue to experience chest pain symptoms even after their SCAD lesions have resolved. In a recent study, coronary microvascular dysfunction was found to be present in most of such patients [88]. This suggests that coronary microvascular dysfunction plays a significant role in the development of post-SCAD chest pain syndrome. However, it is still unknown whether coronary microvascular dysfunction contributes to the development of SCAD.

Histologically, infiltration of eosinophils and mast cells has been found in SCAD lesions [89-92], and has been considered pathognomonic [93]. An infiltration of these cells in an otherwise intact vessel wall could cause a weakening of the wall due to the release of cytotoxic and collagenolytic substances, predisposing to the development of SCAD [19]. However, it is also possible that this infiltration may be just a reaction to the vessel wall injury caused by SCAD [93, 94].

The predominance of women in SCAD cohorts and the finding that SCAD is the most common cause of pregnancy-related myocardial infarction suggest a role of female hormones in its pathophysiology. Estrogen, a female sex hormone, has been found to carry many different functions, including vasodilatation, angiogenesis, and modulation of autonomic function [95]. These functions may be relevant to the development of SCAD in women; however, the exact mechanism remains to be defined. SCAD seems to often happen at a time of significant hormonal fluctuation, such as the post-partum period or in recipients of hormonal therapy [72, 96].

A weakness in the arterial wall appears to be the common predisposing factor in SCAD. Many different disorders that impair the vascular wall integrity have been reported in patients with SCAD. Among these conditions, fibromuscular dysplasia (FMD) is the most common [19]. FMD is a disease of small and medium-sized arteries, characterised by abnormal cellular proliferation and disorganisation of the connective tissues of the vessel's wall [97]. The resulting weakness in the arterial wall may predispose to SCAD. In addition to dissections, FMD can also manifest as focal stenosis, beading lesions of the arteries, aneurysms, and tortuosity [98, 99]. Similar to SCAD, most patients with FMD are female (80%-90% [99, 100]). FMD is present in 17% to 86% of patients with SCAD [101-105]. In a meta-analysis of 2172 patients, FMD was present in 68% of patients with SCAD [106]. Although the prevalence of FMD is high among patients with SCAD, it is not the same the other way around. In a study on 921 patients with FMD, only 25 (2.7%) had SCAD [98]. Rare heritable vascular disorders have been reported in patients with SCAD, including vascular Ehler-Danlos syndrome, Marfan syndrome, and Loeys-Dietz syndrome [103, 107, 108]. The prevalence of connective tissue disorders in SCAD was low at < 4% ([71, 109, 110].

Coronary artery tortuosity is associated with SCAD. It is likely that the weakened connective tissue of the arterial wall that predisposes to SCAD also predisposes to arterial tortuosity. A study by Eleid et al on 246 patients with SCAD reported that 78% of patients with SCAD had coronary tortuosity compared to 17% in the control group [109]. In the same paper, Eleid et al proposed a new classification system for coronary artery tortuosity, which ranges in severity from mild to severe. A high level of coronary tortuosity was found to be associated with a higher risk of SCAD recurrence [109]. Tortuosity was more commonly found in non-culprit arteries rather than culprit ones.

However, 80% of SCAD recurrence happened in a tortuous segment [109]. Severe coronary artery tortuosity may impair flow and increase the risk of myocardial ischaemia, especially during high-flow conditions such as exercise [111].

Genetic susceptibility for SCAD

Familial cases of SCAD, including in identical twins, have been reported [112, 113]. Although these cases are relatively uncommon, they raise the possibility of a genetic element in the development of SCAD. Some rare heritable vascular diseases, characterised by reduced vascular wall strength, have been reported in patients with SCAD. These include vascular Ehlers-Danlos syndrome (vEDS) [103, 107], Marfan syndrome [103], Loeys-Dietz syndrome (LDS) [108], Nail-Patella syndrome (NPS) [114], and autosomal dominant polycystic kidney disease (ADPKD) [115, 116]. Genetic studies of various nature, including targeted gene screening, whole exome sequencing, and whole genome sequencing, have been performed [103, 117, 118].

At the level of targeted screening, several mutated genes were reported: COL3A1 (pathogenic for vEDS), SMAD3 (pathogenic for LDS), LMX1B (pathogenic for NPS), PKD1 (pathogenic for ADPKD), FBN 1 (pathogenic for Marfan syndrome), CBS, TLN1, and COL4A2, with mutations in COL3A1 being the most common [103, 117, 119-122]. A recent study on patients with SCAD investigated the prevalence of 25 genes known to be pathogenic for aortic aneurysm and dissection. Out of these genes, only the SMAD2 reached significant enrichment after false discovery rate correction in single-gene burden analysis. On combined-gene burden analysis, the six LDS genes (TGFBR1/2, SMAD2/3, TGFB2/3) also reached a significant status. However, none of these patients had a clinical diagnosis of LDS, suggesting a sub-clinical phenotype.

Recently, mutations in the prostaglandin I_2 receptor (PTGIR) gene, which plays a key role in vascular remodelling, were found to be associated with FMD in an exome study. However, on targeted sequencing of patients with SCAD, these mutations did not pass the burden test (p=0.12) [123].

An exome sequencing study in China reported a significant association of SCAD with the TSR1 gene [124]. TSR1 encodes a protein involved in the assembly of the 40S ribosomal subunit. However, a significant limitation of this study was the inclusion of atherosclerotic coronary artery dissection (ACAD), which may contribute to the unusually low number of female patients (at only 17.6%). It is also unclear how a defect in ribosome assembly relates to the development of SCAD.

A large genomic-level study has identified enrichments in the pathogenic or likely pathogenic mutations in 7 genes [125]. However, no single gene achieved statistically significant status. In gene-set analysis, the group of 6 genes achieved statistical significance (PKD1, COL3A1, SMAD3, FBN1, TLN1, TSR1). Another genomic study on a mother-daughter pair with SCAD identified the gene F11R as potentially related to the development of SCAD in this pair [126]. F11R is a gene encoding a component of the tight intercellular junction.

Overall, genetic testing for rare gene variants in patients with SCAD has been of relatively low yield. This has prompted research into more common genetic variants. The PHACTR1/EDN1 is a genetic locus on chromosome 6q24, reported to be associated with the risk of CAD [127]. EDN1 is involved in the biosynthesis of endothelin 1, a potent vasoactive peptide produced by endothelial cells [128]. Interestingly, this locus was also found to be related to FMD [129], migraine [130], and cervicocerebral artery dissection [131], conditions which is related to, or similar to SCAD. A genetic study focusing on the allele rs9349379 in this locus in patients with

SCAD was performed [132]. It was found that the common allele rs9349379-A was associated with a higher risk of both SCAD and FMD, while the minor allele rs9349379-G was associated with atherosclerotic CAD [133]. Genome-wide association studies (GWAS) have also confirmed the role of the PHACTR1 locus [134], while other loci were also identified. These loci contain following genes: ECM1 (encodes a secretory glycoprotein which interacts with matrix proteins, mediating many processes including angiogenesis), C1orf54 (encodes a protein of unknown function), ADAMTSL4 (encodes an extracellular matrix protein), MRPS21 (encodes a protein making up the 28S ribosomal subunit), LPR1 (encodes a cell-membrane receptor which plays a role in focal adhesions disassembly), LINC00310 (non-coding RNA, unknown function), FBN1 (encodes a component of extracellular microfibrils) [134, 135]. Disorder of ADAMTSL4 was known to cause isolated ectopia lentis [136], while the inactivation of LPR1 in mice led to arterial aneurysm formation due to disruption of elastic fibers [137]. A rabbit model of carotid artery aneurysm demonstrated high expression of C1orf54, although its function in human is still unknown [138].

In summary, only a small proportion of patients with SCAD have an identifiable mutation pathogenic for a hereditary connective tissue or vascular disease. At the same time, some more common gene variants are associated with an increased risk of SCAD. Most of those genes affect the risk of SCAD due to their role in maintaining the integrity of the vascular wall, although in some cases, the mechanism for their association with SCAD is still unknown.

Natural progression of SCAD

Most cases of SCAD heal spontaneously. In studies where patients with SCAD had repeat coronary imaging, the rate of healing was 73% to 100% [72, 110, 139, 140]. As patients who underwent a repeat angiogram were more likely to experience symptoms

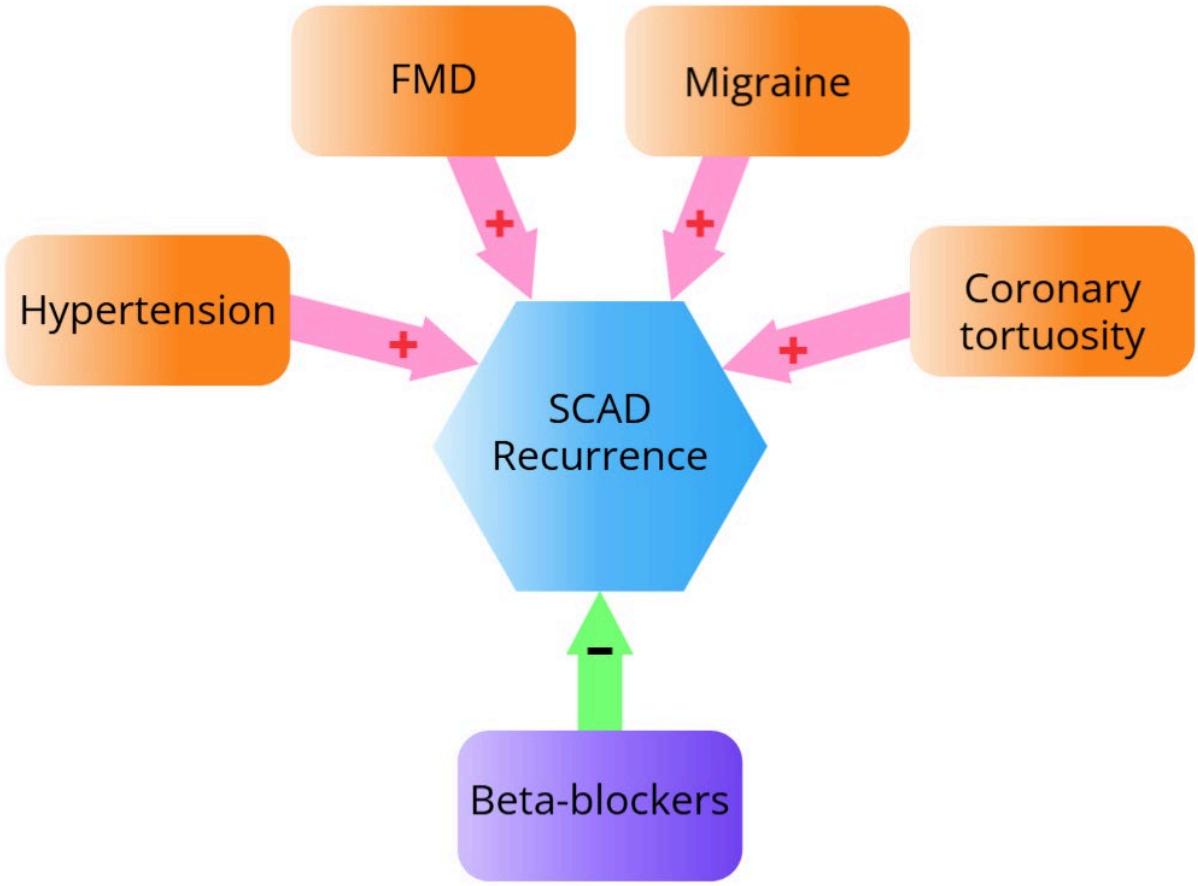
compared to those who did not, it is reasonable to assume that the rate of healing in those who did not undergo a repeat angiogram is at least similar to, if not higher than, that of those who did. Overall, the rate of spontaneous healing in SCAD is likely to be high.

The mortality rate of SCAD varied significantly between studies, from 0% to 8.7% [7, 25, 40, 141]. In the Canadian SCAD Registry, in-hospital mortality was 0.1% and total three-year mortality was 0.8% [58]. In a systematic review and meta-analysis of 2817 patients, the pooled estimate of SCAD mortality was 1% with a mean follow-up of 33 months [142]. In the same study, male sex (odds ratio [OR] 3.5, 95% confidence interval [CI] 1.22-10.03) and smoking history (OR 15.32; 95% CI 2.88-81.41) were independent predictors of mortality in patients with SCAD.

In the Canadian SCAD Registry, the rate of in-hospital major adverse cardiovascular events (MACE) was 8.8% and total MACE after three years of follow-up was 8.4% [58]. The Spanish SCAD Registry reported a higher rate of MACE of 13.0% with a median follow-up of 29 months (interquartile range 17-38) [33].

SCAD can recur after the index event in the same or different coronary artery, causing a recurrent myocardial infarction. The rate of recurrence differed among various studies, ranging from 3.5% to 29% [8, 28, 58, 72, 140]. In a systematic review and meta-analysis of 1408 patients, the recurrence rate was 5.49 per 100 person-years [106]. The recurrent SCAD can occur over 10 years after the initial SCAD [143]. Multiple clinical factors have been reported to be associated with increased risk of recurrence, including hypertension, FMD, coronary artery tortuosity, and migraine [40, 109, 144]. However, the associations were not consistent across different studies. In a systematic review and meta-analysis, beta-blockers were the only class of pharmacotherapy associated with a reduction in SCAD recurrence [145].

Figure 2 – Factors associated with spontaneous coronary artery dissection recurrence



FMD: Fibromuscular dysplasia; SCAD: Spontaneous coronary artery dissection

Clinical presentation of SCAD

Patients with SCAD most commonly present with an ACS. In the Spanish SCAD Registry of 318 patients, 94% of the patients presented with ACS, with 39% having ST-elevation myocardial infarction (STEMI), 53% having non-ST-elevation myocardial infarction (NSTEMI), and 2% having unstable angina [66]. Other presentations included atypical chest pain (1%), syncope (1%), ventricular arrhythmia (2%), and

sudden cardiac death (1%) [66]. Sudden cardiac death is rare in SCAD. In an autopsy study on 5325 cases, only 18 (0.3%) were diagnosed with SCAD [146].

In many cases of SCAD, a triggering event could be identified [71, 110]. This can either be an emotional stress or a physical one (heavy lifting, strenuous physical activities with or without Valsalva manoeuvre). In the Canadian SCAD registry, 66.4% of patients reported a potential precipitating stressor: 50.3% emotional stress, 28.9% physical stress, 9.8% heavy isometric activities, and 0.3% cocaine or amphetamine use [71]. Physical stress is more common in men, while emotional stress is more common among women [147]. It is possible that the increased vascular shear stress associated with a hyper-catecholaminergic state and/or Valsalva-like manoeuvres could precipitate SCAD in a susceptible artery [19].

In a study in Canada on 1173 patients with SCAD, men were younger than women at the age of their SCAD event (mean age 49.4 vs 52.0, p =0.01) and were less likely to have fibromuscular dysplasia (27.8% vs 52.7%, p=0.001), depression (9.8% vs 20.2%; P = 0.005), or emotional stress (35.0% vs 59.3%; P < 0.001) [68]. Men were more likely to have isometric physical stress as a trigger, compared to women (40.2% vs 24.0%; P = 0.007) [68]. There were no differences in in-hospital events or major adverse cardiovascular events on follow-up (7.3% vs 12.7%; P = 0.106) [68].

Diagnosis of SCAD

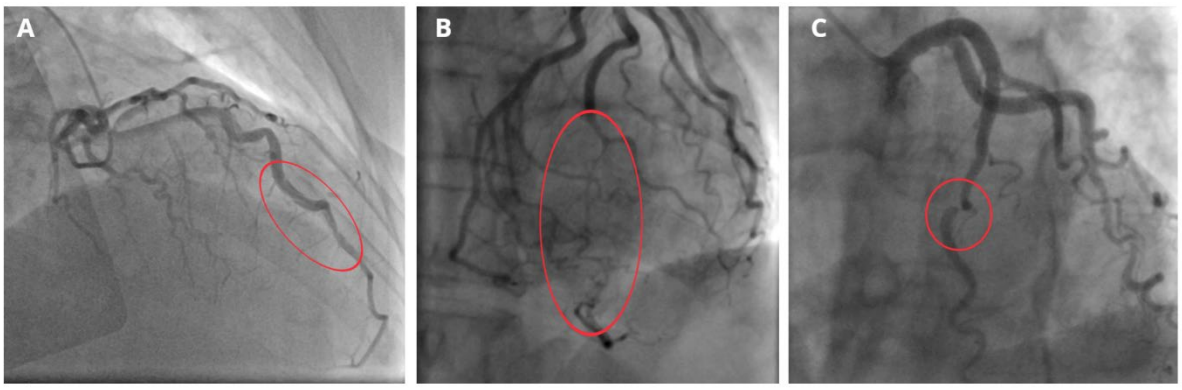
Diagnosis of SCAD is reliant on invasive coronary angiography, with SCAD Type further divided into three distinct angiographic types, as proposed in 2014 by Saw et al [148].

Type 1: There is communication between the true lumen of the coronary artery and the haematoma, forming false lumen(s). Contrast can be seen in both the true and false lumens, with a flap separating the two. This is the angiographically pathognomonic type of SCAD.

Type 2: Intramural haematoma extending along the affected coronary artery, typically > 20 mm. Contrast is seen in the true lumen only. The angiographic appearance is of a diffuse stenosis, usually starting from the middle or distal segment of the vessel. The intramural haematoma, and thus the stenosed section of the vessel seen on angiogram, may or may not extend all the way to the tip of the vessel. Saw et al also suggested the following additional criteria to diagnose type 2 SCAD [110]: a) no change in the stenosis after the intracoronary injection of nitroglycerin, with no atherosclerotic lesions in other vessels, or b) subsequent coronary angiogram demonstrates resolution of the stenosed segment, or a prior angiogram demonstrated normal vessel, or c) intracoronary imaging demonstrates intramural haematoma and double lumen.

Type 3: Intramural haematoma affects a short segment of the coronary artery only, typically < 20 mm. This type can mimic an atherosclerotic plaque and is the most challenging to diagnose. Factors favouring a diagnosis of SCAD, rather than atherosclerosis, include location at the middle to distal part of a vessel and normal-appearing vessels elsewhere. In many cases, a diagnosis cannot be reliably made from angiogram alone. Intravascular imaging, such as Intravascular Ultrasound (IVUS) or Optical Coherence Tomography (OCT) can help differentiate between SCAD and other types of lesions.

Figure 3 – Radiographic types of spontaneous coronary artery dissection.



Panel A: Type 1 SCAD, characterised by double lumens with an intimal flap; Panel B: Type 2 SCAD, characterised by a long (> 20 mm) segment of luminal stenosis; Panel C: type 3 SCAD, characterised by a short (< 20 mm) segment of luminal stenosis. Images obtained from the ANZ-SCAD Registry.

In 2016, Saw et al introduced two more subtypes [149]: Sub-type 2A, where the haematoma does not extend to the tip of the vessel (the stenosed segment is "sandwiched" between normal-appearing segments), and sub-type 2B, where the haematoma extends all the way to the tip. This classification system was widely accepted and used by international professional societies [79, 93].

Another type of SCAD, type 4, was introduced in 2017 by Al-Hussaini et al [150]. In this type, the haematoma causes a total occlusion of the lumen, with an abrupt cut-off appearance on the coronary angiogram. Typically, this type is diagnosed when a subsequent angiogram demonstrates spontaneous resolution of the obstruction, in keeping with the natural progression of SCAD. This type has not been widely used in practice and has not been endorsed by the American Heart Association.

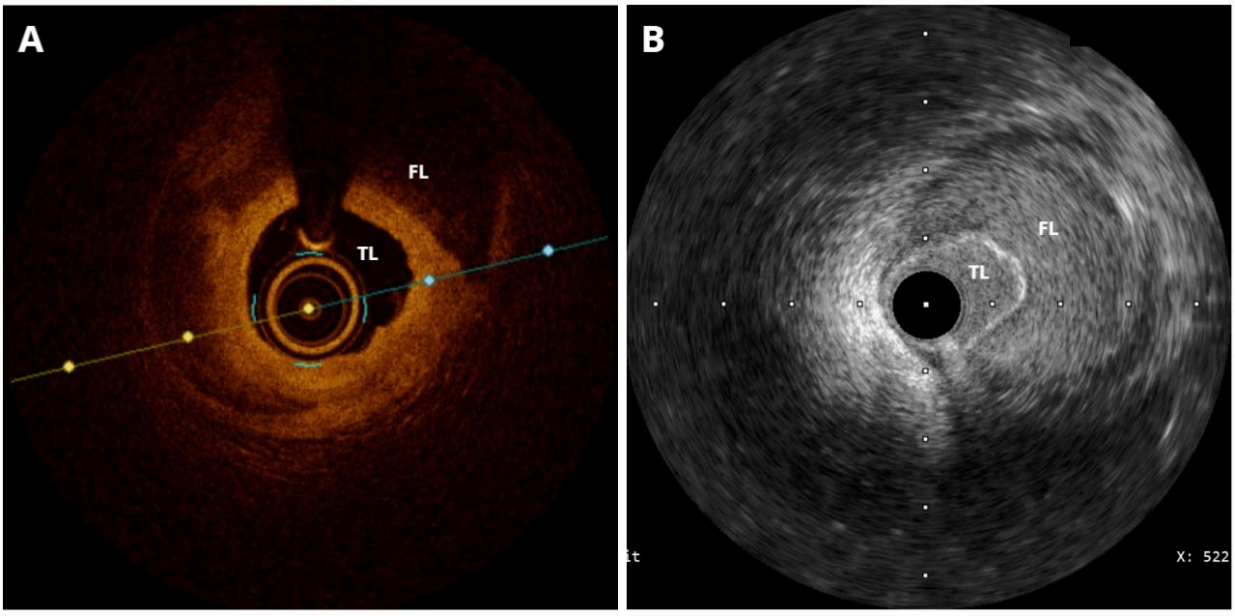
Table 1 – Characteristics of SCAD types and subtypes on coronary angiography

SCAD subtypes	Characteristics
I	Free communication between the true and false lumens. Contrast is present in both the true and false lumens with a visible dissection flap.
II	Intramural haematoma causing a long stenosis (> 2 cm) of the artery. Contrast is present in the true lumen only.
IIa	The intramural haematoma does not extend to the tip of the artery.
IIb	The intramural haematoma extends to the tip of the artery.
III	Intramural haematoma causing a short stenosis (< 2 cm) of the artery, resembling atherosclerotic plaque. Contrast is present in the true lumen only.
IV	Intramural haematoma fully occluding the true lumen. Contrast is cut off at the point of full occlusion.

The diagnosis of SCAD may be challenging. Apart from type 1 SCAD, which is pathognomonic and usually easy to identify, other types are often more challenging to diagnose, particularly types 3 and 4. The proportion of type 1 SCAD is relatively low. In a cohort study of 750 patients, 29.0% had type 1, 60.2% had type 2 (34.2% type 2A, 25.9% type 2B), and 10.8% had type 3 SCAD [58]. Type 4 SCAD was reported at 24% in a recent small study that consisted of 21 patients [53]. The following features may help to differentiate SCAD from atherosclerotic lesions: long (>10 mm), tubular

stenosis, involvement of the middle or distal vessel, coronary tortuosity, no coronary calcification, and no disease in non-culprit vessels. Intravascular imaging (IVI) modalities, including IVUS and OCT, may assist in the diagnosis of SCAD. For the purpose of SCAD diagnosis, OCT is more advantageous than IVUS due to its higher spatial resolution (axial 12 - 18 μm and lateral 20 -90 μm, compared to axial 150 - 200 μm and lateral 150-300 μm of IVUS) [151]. However, the use of OCT requires intracoronary injection of contrast (10-12 ml to scan a 50 mm to scan a 50 mm long segment [152, 153]), which poses the risk of causing propagation of the dissection or haematoma. However, the contrast injection in the modern OCT technique was shown not to be more harmful than that of a usual coronary angiogram acquisition [154]. In a small series of 11 patients with SCAD who underwent OCT, no complication was reported [155]. In a larger cohort of 63 patients who had OCT, 7.9% developed an OCT-related complication, none of which resulted in a major adverse outcome [80]. IVI use may be limited in tortuous vessels or distal vessels, which are commonly involved in SCAD.

Figure 4 – Intravascular imaging of spontaneous coronary artery dissection



Panel A: Optical coherence tomography image; Panel B: Intravascular ultrasound image; FL: False lumen; TL: True lumen; Images obtained from the ANZ-SCAD Registry.

Computed tomography coronary angiogram (CTCA) can also be used to diagnose SCAD. Features of SCAD on CTCA include: abrupt luminal stenosis, intramural haematoma, tapered luminal stenosis, and dissection [156]. Compared to an invasive coronary angiogram, CTCA has the significant advantage of being non-invasive, thus negating the mechanical risks of an invasive investigation. One group of authors have advocated the use of CTCA as the initial diagnostic approach in patients with ACS who are stable and have a high pre-test probability of SCAD [157]. However, the main disadvantage of CTCA is its lower resolution – approximately 0.5 mm compared to 0.1-0.2 mm of an invasive coronary angiogram. CTCA is also more dependent on heart rate to obtain quality images. In a small case series of 18 SCAD lesions, CTCA correctly diagnosed SCAD in 14 (a true positive rate of 77.8%), with most of the missed

lesions being small or located in the distal vessels [158]. In another study of 32 patients with SCAD, the overall sensitivity of CTCA was 62.5%, with 100% sensitivity for proximal SCAD and 58.6% for distal SCAD [159]. In the acute phase of ACS, CTCA has been advocated as an adjunct to invasive coronary angiography when the diagnosis remains uncertain. In this case, the lack of coronary atherosclerosis may support the diagnosis of SCAD. CTCA may also be considered when repeat coronary imaging is deemed necessary, particularly if the initial SCAD lesion involved a large or proximal vessel. However, there remains no consensus on the use of CTCA in SCAD at this stage.

Treatment of SCAD

The optimal treatment of SCAD has not been established. It was not until 2018 that professional societies, including the American Heart Association and the European Society of Cardiology, first published their recommendations about the management of SCAD in the form of position papers or consensus statements [79, 93]. These recommendations were based on observational studies and expert opinions. Until now, no randomised controlled trial on patients with SCAD has been published. Anecdotally, some clinicians use treatments recommended for atherosclerotic ACS for patients with SCAD.

Conservative versus invasive treatments

As most SCADs heal spontaneously, a conservative approach is preferred, particularly in patients who are haemodynamically stable and do not have signs or symptoms of ongoing myocardial ischaemia. Invasive intervention should be considered for patients with haemodynamic instability or high-risk anatomy (defined as left main or proximal

2-vessel coronary artery dissection) [93]. Invasive intervention in SCAD involves a higher risk of complications [139]. Patients with SCAD are more prone to iatrogenic (usually related to the catheter) dissection even with coronary angiography only [110, 160, 161]. SCAD usually affects distant and small vessels, which may be challenging or not amenable to stenting [93]. During intervention, the guidewire may inadvertently enter the false lumen [162, 163], or the act of balloon angioplasty or stenting may cause further propagation of the dissection [10]. After intervention, the resorption of the haematoma may lead to stent strut malapposition [164]. In a systematic review comparing revascularisation and conservation in which 11 studies with 631 patients were reviewed, there was no difference in mortality between these two approaches [165].

Where coronary intervention is deemed necessary, a number of techniques have been proposed to treat SCAD. These include: cutting balloons to create a communication between the lumens, thus reducing the pressure of the haematoma, creating fenestrations with a guidewire [166], drug-eluting balloons to seal the intimal flap [167], and stenting with drug-eluting stents or bioresorbable scaffolds [168]. The use of IVI systems, such as OCT and IVUS [168] further help confirm the location of the guidewire (true lumen vs false lumen) and to guide the choice of stent size and stent positioning.

Thrombolysis

Despite the successful use of thrombolysis in some historical cases [169], it can cause progression of the dissection, even coronary artery rupture and cardiac tamponade [170, 171]. Thrombolysis is therefore contraindicated in patients with SCAD [79]. However, patients may receive thrombolysis before the diagnosis is known, as many

patients with SCAD present with ST-elevation MI, where reperfusion is necessary before arrival at the catheterisation laboratory.

Antiplatelets

Antiplatelet agents are the cornerstone in the treatment of atherosclerotic ACS. By suppressing platelet activation and aggregation, they help prevent thrombus formation, minimizing flow obstruction and myocardial ischaemia. However, antiplatelet therapy has been controversial in SCAD, where an intramural haematoma is formed with resulting compression on the true lumen. There is a theoretical risk that they can exacerbate the haematoma or dissection. On the other hand, the exposure of blood to the sub-endothelial tissues in SCAD creates a prothrombotic state, with both intraluminal and intramural thrombus found by OCT study in patients with SCAD [172].The use of antiplatelet therapy may reduce this burden, thus reducing the risk of intraluminal obstruction in the acute phase [173]. There are no randomised controlled trials to guide the use of antiplatelets in patients with SCAD, and experts' opinions vary considerably. Recommendations ranged from dual antiplatelet therapy for at least 1 year after SCAD, regardless of the initial treatment strategy (conservative vs invasive) [174], to not using antiplatelet therapy at all [93]. For patients who were managed conservatively, the American Heart Association (AHA) suggested the use of aspirin for at least 1 year. At the same time, the European Heart Association (ESC) advocated for dual antiplatelet use in the acute phase and single antiplatelet use in the long term. However, the duration of these phases was not defined. In a population with a high proportion of women of menstruation age, menorrhagia with long-term antiplatelet use is a potential complication that needs to be considered [175]. For patients who received coronary stents, dual-antiplatelet use for 12 months, then long-term single antiplatelet therapy was recommended [79].

Anticoagulation

The same concerns for antiplatelet therapy discussed above also apply to anticoagulation therapy. There is no indication for the use of anticoagulation in patients with SCAD [79, 93]. However, it can be used if other indications (e.g., atrial fibrillation) are present.

Statins

In a cohort of patients with SCAD, patients who were treated with statins had a higher risk of SCAD recurrence [72]. However, this finding was not reproduced in a larger study [144]. Routine statin use is not needed in patients with SCAD unless there is another clinical indication [79, 93].

Beta-Adrenergic Blockers

Beta-blocker therapy has been found to be associated with reduced SCAD recurrence. In the Canadian SCAD registry, beta-blocker was associated with a nearly threefold lower risk of SCAD recurrence on multivariate analysis (hazard ratio 0.36, 95% confidence interval 0.18-0.73, p=0.004). In a recent systematic review and meta-analysis, beta-blocker therapy was also found to be associated with a lower risk of SCAD recurrence [145]. It is therefore advocated to be used routinely in patients with SCAD [79, 93]. However, the optimal type of beta-blocker, dose, or duration is unknown.

Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB)

ACEI and ARB is recommended for patients with myocardial infarction and left ventricular dysfunction [176-178]. Their use in patients with SCAD who do not have left ventricular impairment has not been established. As hypertension has been

reported to be associated with increased risk of SCAD recurrence, ACEI or ARB could be used to treat hypertension in patients with SCAD [144].

Antianginal therapy

Antianginal medications (including nitrates and calcium channel blockers) may be helpful to control chest pain for patients with ongoing symptoms following SCAD [93]. In some patients who had cyclical chest pain, the use of hormonal intrauterine devices to help control anginal symptoms has also been reported [150].

Cardiac rehabilitation

As strenuous physical activities can trigger SCAD, there have been some concerns about exercising in general, including cardiac rehabilitation activities. However, cardiac rehabilitation has been shown to be safe and beneficial in improving the well-being of survivors [179-181]. It is recommended that all patients with SCAD should be referred to cardiac rehabilitation [79, 93]. Mild to moderate levels of exercise, such as interval training, weight training with low resistance and high repetitions, are recommended for patients with SCAD, while high-intensity exercise, and peak weights with prolonged Valsalva manoeuvre are recommended to be avoided [182].

Contraception and hormone replacement therapy

Female hormones have been implicated in the pathophysiology of SCAD, and cases where SCAD was triggered during hormonal contraception and hormone replacement therapy initiation have been reported [183-185]. However, due to the high prevalence of these hormone therapies in the general population, their association with SCAD is still not established. Exogenous systemic hormones can suppress physiologic estrogen levels. However, whether systemic exogenous hormone use affects SCAD

recurrence is unknown. Due to the lack of data, systemic hormonal therapy is generally avoided in patients with SCAD [96].

Mental health care

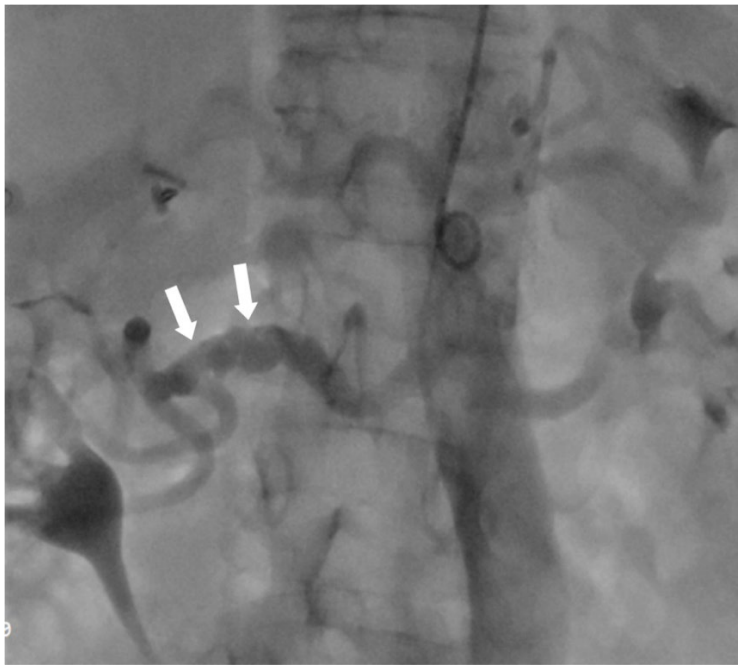
Emotional stress is a known trigger for the development of SCAD, and mental health disorders are highly prevalent among patients with SCAD [16-18, 65, 186, 187]. In one series, nearly 80% of patients reported having a mental health history [17]. Overall, anxiety is the most commonly diagnosed mental disorder, followed by depression, post-traumatic stress disorder (PTSD), and adjustment disorder [16-18, 65, 186, 187]. In qualitative studies, survivors reported high levels of anxiety due to the lack of information about SCAD and the uncertainty regarding its future recurrence [13, 15].

Extra-Coronary Manifestations and Associated Conditions in SCAD

Given the high prevalence of extra-coronary arteriopathies among patients with SCAD, with FMD the most common, screening for these conditions is recommended for all SCAD survivors [79, 93]. Screening can lead to the identification of high-risk vascular abnormalities, which may require early intervention or close surveillance [97, 188, 189]. In a systematic review and meta-analysis, FMD was found to be associated with increased risk of SCAD recurrence (relative risk 2.02; 95% CI, 1.03-3.94; P = 0.04) [145]. Moreover, FMD has been found to be an independent predictor of MACE [58]. The recommended screening modality is with head-to-pelvis computed tomography (CT) angiography, with other methods including invasive angiography (Figure 5) [149], [104], magnetic resonance angiography (MRA), and duplex ultrasound [101]. Patients should be informed about the risks of screening, including false negatives, false positives, and the risk of invasive procedures that may be used to treat the identified vascular abnormalities [93, 190]. Several factors may hinder the adoption of extra-

coronary arteriopathies screening in patients with SCAD. In a relatively young population, the additional cost and exposure to ionising radiation during screening are matters of concern, particularly when data on the cost-effectiveness and risk-benefit ratio of such screening are still limited. The availability of screening modalities, including CT angiography and MRI angiography, is another issue, with rural sites likely to be more limited compared to metropolitan areas.

Figure 5 – Typical “string of beads” appearance (white arrows) of fibromuscular dysplasia of the right renal artery, diagnosed during an invasive coronary angiogram in a patient with SCAD and NSTEMI. Image obtained from the ANZ-SCAD Registry



Preamble to the next chapter

This chapter introduces the rationale, scope, and aim of this thesis, followed by a scoping review of SCAD. Despite its clinical significance, SCAD remains a poorly understood condition, and its optimal treatments remain unestablished. The next chapter is a narrative review of SCAD and its management from a clinician’s perspective.

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Author contributions statement

This contribution statement is to endorse the role of Quan Minh Dang as the first author and the principal contributor in the preparation and submission of the following manuscript:

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Task and Role of Co-Authors

Literature review **QD**

Research question **QD/SZ**

First draft **QD**

Critical revision **All authors**

Study supervision **SZ**

Sincerely,

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CHAPTER 2: A NARRATIVE REVIEW ON THE PATHOGENESIS OF SPONTANEOUS CORONARY ARTERY DISSECTION, IT'S CLINICAL DIAGNOSIS, AND MANAGEMENT

Aims:

- To summarise the current understanding of SCAD's pathogenesis, aetiology, epidemiology, diagnosis, and treatment of SCAD

Preface:

Recent data have suggested that SCAD is more common than was once thought. SCAD is the cause of ACS in up to one-third of young women and the leading cause of pregnancy-related ACS. This chapter reviewed the current literature on SCAD with a focus on current understandings about its clinical diagnosis and management. This helped lay the groundwork for later chapters in this thesis.

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Spontaneous coronary artery dissection: a clinically oriented narrative review

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Spontaneous coronary artery dissection (SCAD) is an important cause of acute coronary syndromes (ACS), with a higher incidence in younger female patients. It is also associated with pregnancy, delivery, and the post-partum period. Despite an exponential rise in the volume of SCAD-focused research and publications within the past decade, SCAD is still a poorly understood condition, with a paucity of randomised controlled trial data. This review discusses the pathophysiology, clinical presentation, diagnosis and management of SCAD alongside areas for future research.

Spontaneous coronary artery dissection (SCAD) is an increasingly recognised cause of acute coronary syndrome (ACS) in younger women. SCAD was first described in the British Medical Journal in 1931, in a 42-year-old woman who developed severe chest pain and died suddenly; with autopsy finding a ruptured dissecting right coronary artery[1]. Since this first case report, research interest into SCAD has increased substantially[2]. SCAD has a strong predilection for young and middle-aged women. While the prevalence of SCAD is less than five percent of all ACS, it accounts for a third of cases in women under the age of 50[3–6]. This paper will discuss contemporary understanding of the pathophysiology, clinical presentation, diagnosis and management of SCAD.

Definition and classification of SCAD

SCAD is typically characterised by the sudden formation of an intramural haematoma between any of the three layers (intima, media, and adventitia) of the coronary artery wall, forming a false lumen (Fig. 1). It is not related to atherosclerotic, traumatic, or iatrogenic causes[7,8]. An intimal tear or fenestration may form a communication between the intramural haematoma and true lumen of the artery. SCAD may cause abrupt mechanical obstruction to coronary blood flow, resulting in acute myocardial infarction (MI), and less commonly, acute cardiac arrhythmia and sudden cardiac death.

Invasive coronary angiography (ICA) is the current gold-standard investigation to diagnose SCAD. Saw et al.[9,10] proposed three types of SCAD based on angiographic appearance (Table 1, Fig. 2). In type 1 SCAD, contrast is visible in both the true and false lumens giving the pathognomonic appearance of multiple lumens on angiography. In type 2 and type 3 SCAD, contrast can be seen in the true lumen only with the appearance of a diffuse (type 2) or short (type 3), often tubular, stenosis. It may be difficult to differentiate type 3 SCAD from an atherosclerotic lesion on coronary angiography alone and intravascular ultrasound (IVUS) or intracoronary optical coherence tomography (OCT) may be required to confirm the diagnosis. Type 2 SCAD can be further sub-classified into type 2a, where the haematoma is sandwiched between normal artery segments proximal and distal to the affected segment, and type 2b, where the SCAD/haematoma extends to the very distal aspect of the vessel. In 2017, Al-Hussani et al.[11] proposed a type 4 SCAD, where the coronary artery is completely occluded. Type 4 SCAD can be difficult to differentiate from other causes of coronary occlusion and can usually only be diagnosed by additional intracoronary imaging after vessel opening, or subsequent angiography showing full vessel healing[11]. Saw et al.[12] found ~30% of SCAD affected arteries to be occluded distally however, a long segment of diffuse narrowing prior to the occlusion would usually be seen, meaning these cases would be classified as 2b. A registry study of 1002 SCAD affected arteries found that the prevalence of type 1, type 2, and type 3 SCAD were 29.0%, 60.2%, and 10.8%, respectively[12].

Epidemiology of SCAD

SCAD was once thought to be a rare condition[13] however, there has been an increased incidence that likely reflects rising awareness amongst clinicians and improved access to intracoronary imaging[7,14]. In published studies, the proportion of SCAD among patients with ACS ranges from 1 to 5%[15–19] of which 80–95% of all SCAD cases are found in women[5–29]. In women under 50 years of age with MI, the prevalence of SCAD is up to 35%[3–6]. In one study, SCAD was one of the most common

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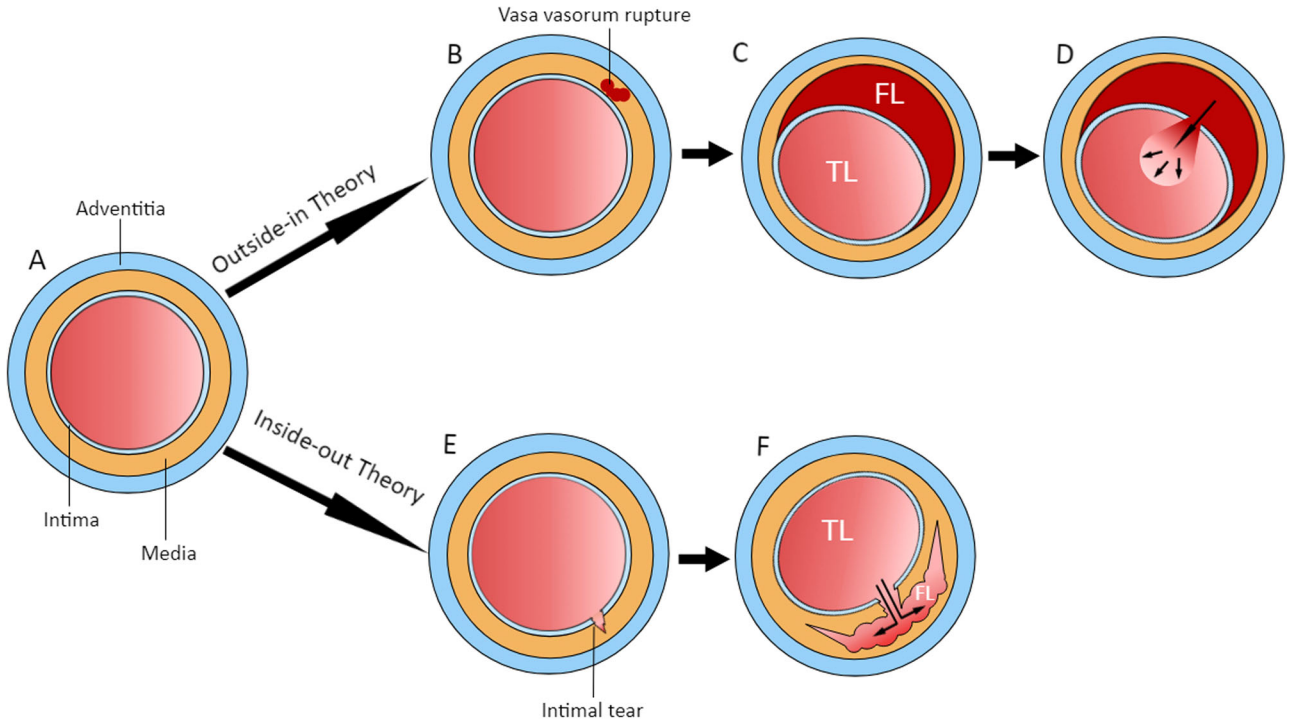

Fig. 1 | Pathophysiology of SCAD. Schematic representation of the cross-section of a normal coronary artery with three layers **A**. In the Outside-in Theory, a vasa vasorum ruptures in the media, causing a small intramural haematoma **B**. This haematoma may increase in size and compress the true lumen **C** and/or result in a rupture of the intima leading to the haematoma emptying into the true lumen **D**. In the Inside-out Theory, a tear first appears in the intima **E**, followed by sub-intimal dissection caused from blood entering from the lumen creating a false lumen. FL false lumen, TL true lumen. The false lumen may expands as the dissection spread further between layers of the arterial wall **F**.

Table 1 | Coronary Angiography Classification of SCAD

Type of SCAD	Description
Type 1	Multi-lumen appearance with visible contrast in both true and false lumens
Type 2 Type 2a Type 2b	Appearance of a diffuse stenosis (> 2 cm) with contrast visible in the true lumen only SCAD does not extend to the tip of the vessel SCAD extends to the tip of the vessel
Type 3	Appearance of a short stenosis (< 20 mm). Contrast visible in the true lumen only, may mimic atherosclerotic lesion
Type 4	Total occlusion of the coronary artery. Need to exclude thromboembolism as a cause and subsequent angiography should demonstrate healing of the vessel in keeping with the natural progression of SCAD

SCAD Spontaneous coronary artery dissection.

causes of pregnancy-associated acute MI, described in 43% of MI cases[20]. This female predominance appears to be relatively consistent across the world, except for the Persian Gulf area, where only 50% of patients with SCAD, in a single study, were reported to be female[21]. The cause of this different gender proportion is not fully understood. Possible contributing factors might include the inadvertent inclusion of atherosclerosis cases, differences in diagnostic criteria, gender-related differences in diagnostic strategies, or ethnicity-related difference in susceptibility.

In multi-ethnic countries like the United States of America or Canada, Caucasians make up about 90% of SCAD registry patients but comprise no more than 70% of the general population[12,22–24]. This over-representation of Caucasian people may reflect selection bias, or true differences in SCAD susceptibility between ethnicities. While studies in China and Japan provided data about SCAD in Asian populations, there is limited data about the occurrence of SCAD in black or Indigenous people[6,25]. One possible explanation is the earlier development of atherosclerosis in indigenous people which may preclude the diagnosis of SCAD[26,27].

Pathophysiology and risk factors for SCAD

There are two main theories about the mechanism of SCAD: the inside-out and outside-in theories (Fig. 1)[7,8]. In the inside-out theory, the initial insult is a tear involving the coronary intimal layer. Blood then dissects to the sub-intimal space to form a haematoma. In the outside-in theory, the initial insult is proposed to be a rupture of the vasa vasorum, leading to a haematoma forming in the arterial wall. This haematoma may then rupture into the true lumen. This is supported by findings on OCT imaging of SCAD cases which showed a lack of communication between the true and false lumen[28–30]. Features suggesting pressurisation in the false lumen includes larger lumen size when indexed to lesion length and absence of contrast in the false lumen even with fenestrations[30]. It is believed that the outside-in theory is the more common mechanism, thus, postulating that bleeding is the primary mechanism rather than dissection/tearing. This observation may change how we manage people with SCAD in the future regarding long term use of antiplatelet therapy.

The observation that SCAD mostly affects young women, and that SCAD is the most common cause of pregnancy-associate MI suggest a role of female hormones in SCAD susceptibility[20]. Oestrogen, a female sex

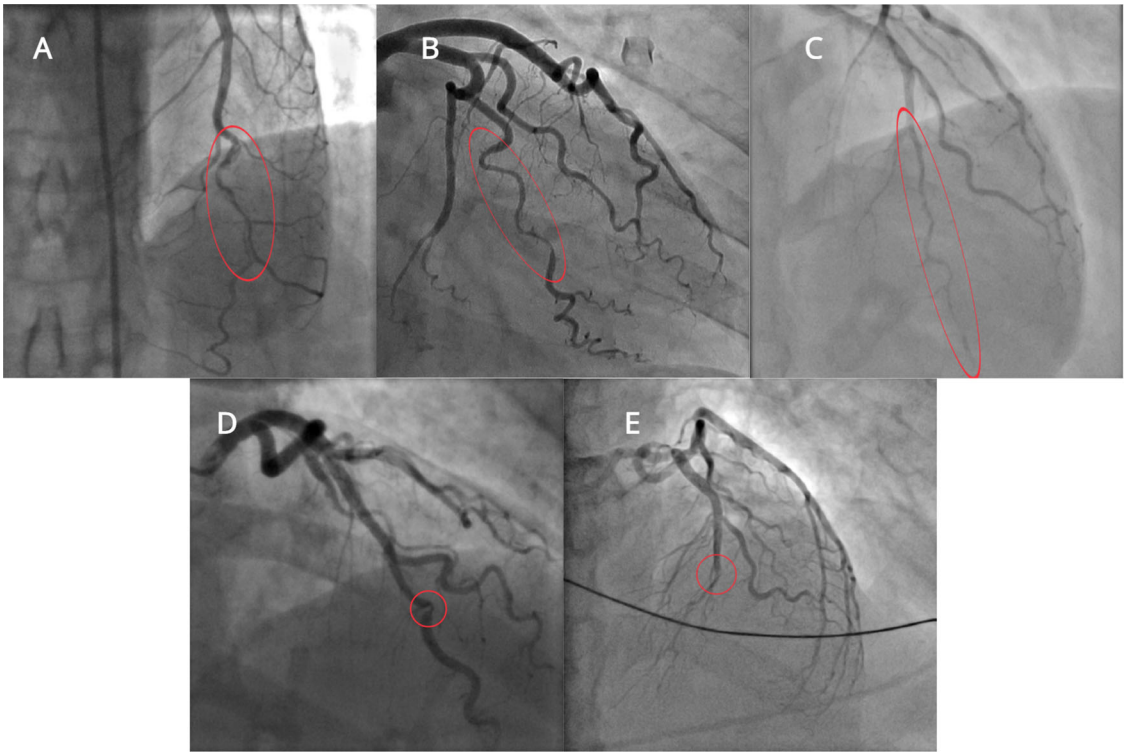

Fig. 2 | Angiographic types of spontaneous coronary artery dissection. A Type 1 SCAD; **B** Type 2 A SCAD; **C** Type 2B SCAD; **D** Type 3 SCAD (confirmed on intracoronary imaging); **E** Type 4 SCAD (completely occluded vessel, confirmed on intracoronary imaging and after repeat angiography showed healing). Images sourced from the ANZ-SCAD Registry[89]. SCAD spontaneous coronary artery dissection.

hormone, has been known to also have effects on angiogenesis, vasodilation, and autonomic regulation[31]. These effects may explain its association to SCAD, although the exact mechanism remains unclear.

Structural weakness in the arterial wall is a predisposing risk factor for SCAD. Multiple arteriopathies have been reported in SCAD cases with the most common one being fibromuscular dysplasia (FMD)[12,32–34]. FMD is an arteriopathy affecting small- and medium-sized arteries characterised by disorganised architecture of the arterial wall without an atherosclerotic or inflammatory cause[35,36]. Multiple studies have shown a high prevalence of FMD and other extra-coronary vascular abnormalities (up to 86%) among patients with SCAD[33,37,38]. As a result, screening for FMD and other extra-coronary arteriopathies has been advocated for in all patients with SCAD.

Rare instances of familial cases of SCAD, including in identical twins, have also been reported[39,40], suggesting genetic susceptibility. SCAD has also been observed in cases of rare inherited vascular diseases, such as Ehlers-Danlos syndrome, Marfan syndrome, and Loey-Dietz syndrome[41–43]. However, this is uncommon and genetic testing targeting rare pathogenic mutations have low yield[7,8]. Low-frequency allele variants were also found be contributed to SCAD, although not pathogenic. In one study, patients with SCAD were found to be more likely to carry rare variants within the fibrillar collagen genes[44]. SCAD has also been found to be associated with multiple common variants with likely complex polygenic interactions[45]. In a genome-wide analysis looking at more common genetic variants, an allele in the PHACTR1 (phosphatase and actin regulator 1) common genetic locus on chromosome 6p24 (rs9349379-A) has been found to be associated with SCAD[46]. Interestingly, this allele is also associated with FMD, which may contribute to the association between these two conditions. A recent genome-wide association meta-analysis has identified 16 risk loci for SCAD and these loci were most enriched in vascular smooth muscle cells and fibroblast[47].

Clinical presentation and natural progression of SCAD

As SCAD tends to cause an acute obstruction of coronary blood flow, ACS is the most common presentation. In a large prospective SCAD registry in Canada, the proportion of ST elevation MI, non-ST elevation MI, and unstable angina were 27.9%, 69.9%, and 0.4%, respectively[12]. In the same cohort, chest discomfort was the most common symptom (91.5%) while arrhythmia was uncommon at 1.1%. Sudden cardiac death is a rare occurrence. In a recent autopsy study of people with sudden cardiac death, only 0.3% was found to have SCAD[48].

Most cases of SCAD heal spontaneously with time. In studies where repeat coronary angiogram was performed following the index SCAD event, healing was reported in the majority of patients at a median of 5 to 39 months[38,49,50]. A recent retrospective study reported the rate of SCAD healing on computed tomography coronary angiography (CTCA) 80 days after the index event to be 71.4%[51]. It should be noted that as repeat coronary angiography would be more likely to be done in patients with recurrent symptoms, the true rate of healing is likely to be higher than the numbers reported in these studies.

Diagnosis and role of multimodality imaging Invasive coronary angiography (ICA)

Catheter-based ICA is the current gold standard test for the diagnosis of SCAD. Useful features to differentiate between SCAD and atherosclerosis plaque are given in Table 2. In cases of diagnostic uncertainty, administration of intracoronary GTN, use of intravascular imaging (where safe and feasible), CTCA, and cardiac magnetic resonance imaging can be useful. The importance of diagnostic clarity affords appropriate management, which in SCAD is different to the management of atherosclerotic disease.

Intracoronary imaging in SCAD

Intracoronary imaging modalities, including IVUS and OCT, are not routinely performed in all cases of SCAD but may be useful in diagnostic

Table 2 | Useful characteristics to differentiate between SCAD and atherosclerosis on invasive coronary angiography

Characteristics	SCAD	Atherosclerosis plaque
Lesion appearance	Linear, tubular, contrast staining of double lumen	Irregular
Usual location	Mid to distal	Proximal
Non-culprit coronary arteries	Normal arteries, free of significant stenoses	Multiple stenoses in coronary arteries
Length of lesion	Usually >10 mm	<10 mm
Calcification	Uncommon	Possible
Coronary artery tortuosity	Common	Less common

SCAD Spontaneous coronary artery dissection.

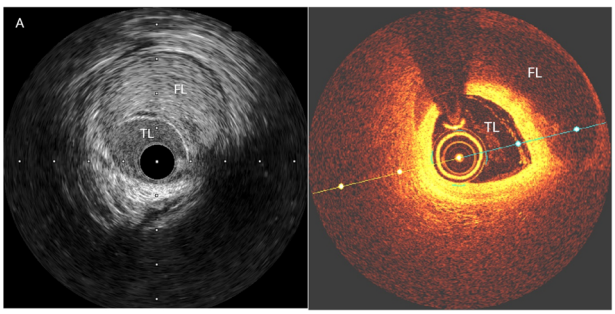

Fig. 3 | Intracoronary imaging findings of spontaneous coronary artery dissection. A intravascular ultrasound image of SCAD; **B** Optical coherence tomography image of SCAD. Images sourced from the ANZ-SCAD Registry[83]. SCAD spontaneous coronary artery dissection, FL false lumen, TL true lumen.

uncertainty and to guide management. In one study, OCT confirmed the diagnosis in 11 out of 17 patients with angiographically diagnosed SCAD[52].

Both imaging modalities, OCT and IVUS, have advantages and disadvantages in the setting of SCAD. OCT has higher spatial resolution, with a greater ability to visualise an intimal tear (Fig. 3). IVUS has better depth penetration and is therefore more useful in larger vessels. IVUS has the additional advantage of not requiring contrast injection during image acquisition as contrast injection risks propagation of the haematoma. In one study of 63 patients with SCAD who underwent OCT, 7.9% had OCT-related complications, but none resulted in a major adverse cardiac event[30]. Another limitation of these intravascular imaging is the size of these devices (approximately 1 mm), limiting their use in small, tortuous, and distal vessels, areas commonly involved in SCAD cases. In the case of diagnostic uncertainty, particularly in larger, more proximal vessels or type III SCAD, either modality can help confirm the diagnosis. When percutaneous intervention is required in cases of SCAD, intracoronary imaging can confirm wire position (luminal or subintimal), guide stent size and length and reduce the risk of stent malapposition following intramural haematoma reabsorption.

Computed tomography coronary angiography (CTCA) in SCAD

CTCA has the advantage of being a non-invasive diagnostic procedure and can demonstrate the presence of coronary calcification or plaque suggestive of underlying atherosclerosis as the alternative cause of coronary narrowing[53,54]. One report has proposed that CTCA be used as the first diagnostic test in patients with high suspicion for SCAD[55]. In another small case study, CTCA correctly identified SCAD in 14 out of 18 lesions (78%), with most of the missed lesions located in small vessels[53]. This highlights the main limitation of CTCA in SCAD; the lower spatial resolution that limits detection of SCAD in smaller vessels and therefore, prevents CTCA from excluding the diagnosis. Therefore, CTCA as a primary diagnostic strategy is limited and it remains an adjunctive test to ICA in people with suspected SCAD. An emerging role for CTCA in SCAD is in the long-term follow-up where it has been shown to demonstrate large vessel healing. In a recent study, the sensitivity and specificity of CTCA in detecting unhealed SCAD lesions were 72% and 53.8%, respectively[51]. Currently, however, there is no consensus on the optimal use of CTCA as a follow-up modality.

Acute management

As most cases of SCAD heal spontaneously, where possible, a conservative approach should be used. Percutaneous Intervention carries significant risk due to the higher chance of iatrogenic (catheter-induced) coronary dissection, and wiring, ballooning, or stenting can all promote propagation of the dissection or intramural haematoma[56]. Guidewires and/or stents may inadvertently be placed into a false lumen and stent sizing may be challenging due to the presence of a large intramural haematoma. This can lead to late stent malapposition, restenosis and stent thrombosis. The American Heart Association consensus document has proposed an algorithm to manage acute SCAD[7]. In the Canadian SCAD registry of 750 patients, 86.4% were managed conservatively, with only 2.3% of these patients subsequently requiring invasive treatment. Urgent revascularisation may be required in the case of haemodynamic instability or high-risk anatomy (left main dissection or double proximal vessel disease). In this instance, both percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) can be considered. When PCI is performed, use of intravascular imaging with IVUS or OCT may be helpful, but the risks should also be considered. This enables identification of the coronary wire in the true lumen, correct stent sizing (1:1) and correct stent length to cover the entire dissected segment. There are several options for PCI. The aims of PCI are to restore coronary flow, control the dissection and subsequent haematoma, thus avoiding proximal and distal propagation. Both the proximal and distal edges of the dissection can be stented with subsequent cutting balloon deployment / stent deployment in the mid segment. Alternatively, a single long stent can be used to ensure adequate coverage into normal vessel (at least 5-10 mm beyond proximal and distal borders of the SCAD lesion). Cutting balloons alone can be used to treat SCAD. These are usually deployed at the site of maximal luminal narrowing or as guided by intravascular imaging where possible. In a recent review of 32 cases of SCAD treated with cutting balloon, restoration of flow to Thrombolysis In Myocardial Infarction (TIMI) 3 were achieved in 93.8% of the cases with distal propagation of the haematoma as the most commonly reported complication (18.8%). In the same review, IVUS was used in 53.1% of the cases and provided useful information to guide the intervention[57]. If CABG is performed, then venous grafts may sometimes be the graft of choice, with the knowledge that the affected vessel will likely heal within a few months, and the graft will subsequently occlude. However, there is limited evidence to support decisions surrounding choice of revascularisation strategy in people with SCAD.

Long-term treatment of SCAD and prevention of recurrence

In one study, the 3-year risk of SCAD extension and recurrence were 3.5% and 2.4%, respectively[58]. There are currently no randomised controlled trial data to guide treatment of SCAD. In 2018, the European Society of Cardiology (ESC) and the American Heart Association (AHA) published their first scientific statements on SCAD, with recommendations on pharmacologic treatments with some variation to treatment of people with atherosclerotic ACS[7,8]. However, the latest 2023 ESC ACS guidelines has the recommendation that patients with SCAD be given the same pharmacologic treatments as other patients with ACS[59].

The role of antiplatelet therapy in SCAD has been controversial. As SCAD involves the formation of an intramural haematoma, there is a theoretical risk of promoting further dissection/ haematoma with the use of antiplatelets or anticoagulants used in ACS. However, SCAD is also a prothrombotic state due to the potential exposure of blood to the sub-

Table 3 | Comparison of management between SCAD ACS and atherosclerotic ACS

Treatment	SCAD ACS	Atherosclerotic ACS
Antiplatelets	Single antiplatelet therapy or DAPT for the first 3 months is reasonable. DAPT if stenting	DAPT for 12 months
Statins	No, unless another indication	Yes, Moderate to high dose
Beta-blocker	Yes, Lifelong if tolerated	Yes, Usually at least 12 months
ACEI or ARB	Used for LVEF impairment or hypertension	Yes
Cardiac rehabilitation	Yes	Yes
Screening for FMD	Yes	No

ACEI angiotensin converting enzyme inhibitor, *ACS* acute coronary syndrome, *ARB* angiotensin receptor blocker, *DAPT* dual antiplatelet therapy, *FMD* fibromuscular dysplasia, *LVEF* left ventricular ejection fraction; *SCAD* spontaneous coronary artery dissection.

intimal tissue, and reduced coronary flow from true lumen obstruction. Thrombus formation both in the haematoma and the true lumen has been observed[60]. Antiplatelet use may therefore be beneficial in reducing this thrombus burden. In their scientific statements, the AHA and ESC suggested at least a single antiplatelet agent (aspirin), to be used acutely. In a European observational study, MACE at one year occurred in 18.9% with dual antiplatelet use vs 6% with single antiplatelet use in conservatively managed patients (hazard ratio [HR] 2.62, 95% confidence interval [CI] 1.22–5.61, $p = 0.013$)[61]. An observational study on 327 patients with SCAD found that aspirin lowered the risk of SCAD recurrence on univariate analysis (HR 0.36, 95% CI 0.18–0.73, $p = 0.004$) but not on multivariable analysis[62]. In patients treated with PCI, dual antiplatelet therapy according to current guidelines is recommended.

Based on observational registries, the most common practice worldwide has been to treat people with SCAD with dual antiplatelet therapy (usually aspirin and clopidogrel) for 3 months, followed by single antiplatelet therapy (usually aspirin) lifelong[63]. However, even single antiplatelet therapy can create problems in younger female patients, with menorrhagia a frequent adverse event[7,8]. In these cases, individual case-by-case discussion is needed, given the current lack of efficacy data supporting antiplatelet therapy following confirmed SCAD. Currently no randomised trial data is available to guide management. The Beta-blockers and Antiplatelet agents in patients with Spontaneous Coronary Artery Dissection (BA-SCAD) trial is currently enroling and will address this important and unresolved knowledge gap.

The use of anticoagulation in the acute phase carries the same considerations as discussed in the antiplatelets section above. In the acute settings, anticoagulation is usually commenced prior to coronary angiography. In the absence of other indications, it was recommended that anticoagulation be stopped once a diagnosis of SCAD has been made[7,64].

In a systematic review of n = 4206 patients with SCAD, beta-blockers were found to be significantly associated with a reduced risk of SCAD recurrence after adjustment for confounders; RR of 0.51 (95% CI 0.33 -0.77, $P = 0.0013$)[65]. Beta-blockers have therefore been recommended in all patients with SCAD[7,8]. Once again, side effects of fatigue or reduced exercise intolerance are particularly common in younger patients with SCAD and are often a limiting factor in the ongoing use of beta-blockers.

In a retrospective study ($n = 87$, median 47 months of follow up) statin use was found to be associated with increased SCAD recurrence; 50% vs 8%, $p = 0.022$[66]. However, this was not reproduced in other studies, and a systematic review ($n = 295$) did not find an association between statins and recurrent SCAD[65]. Therefore, while statins are not routinely recommended for people with a confirmed diagnosis of SCAD, they can be used if the diagnosis is unclear, or the patient has hypercholesterolaemia, or atherosclerosis seen on ICA or CTCA. Similarities and differences in management between ACS secondary to SCAD versus atherosclerotic-related ACS is summarised in Table 3.

Patients with SCAD-related ACS and left ventricular ejection fraction (LVEF) impairment should be treated with Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor antagonists (ARB) in keeping with current guidelines[59]. The use in patients without LVEF impairment has not been well established. As untreated hypertension has been shown to be a risk factor for SCAD recurrence, ACEI or ARB could be considered as an option to treat hypertension[65].

Post-SCAD chest pain is a common issue affecting more than half of SCAD survivors[7]. This can be broadly divided into (i) acute chest pain, which should be evaluated in a hospital setting with serial ECGs and cardiac enzyme tests, and (ii) sub-acute or chronic chest pain, which could be managed in an out-patient setting. Chronic chest pain post SCAD could be related to ongoing ischaemia due to non-healing of SCAD, microvascular dysfunction, or unknown causes. In a recent study of 17 survivors with chronic chest pain despite confirmed angiographic healing of SCAD, more than 70% were found to have microvascular dysfunction as indicated by abnormal coronary flow reserve or index of microcirculatory resistance[67]. Anti-anginal medications, such as nitrates or calcium channel blockers could be considered to treat chronic post SCAD chest pain. Protocols for the evaluation and management of chest pain post SCAD have been proposed by the American Heart Association and American College of Cardiology[7,64].

Pregnancy and SCAD

SCAD is one of the most common causes of MI in pregnant women with the post-partum period the most at-risk period[68]. Pregnancy or post-partum SCAD has a 4% in hospital mortality rate. From published studies, pregnancy-related SCAD (P-SCAD) usually has higher incidences of ST elevation myocardial infarction, reduced left ventricular ejection fraction, involvement of the left main artery or multivessel SCAD[20,68–70]. In the Canadian SCAD registry, peripartum status was found to be an independent predictor of 30-day and 3-year MACE[12,58]. P-SCAD is best managed with a multidisciplinary team approach. In women who are pregnant, breastfeeding or planning a pregnancy, aspirin is safe and can be continued. Most beta-blockers are safe in pregnancy (excluding atenolol)[71]. As most medications have not been meaningfully tested in pregnancy, other commonly used SCAD medications should be used with caution in pregnancy or are not recommended during pregnancy or breastfeeding including P2Y12 inhibitors such as clopidogrel (category B) or ticagrelor (category C), statins (category X), and ACEI/ARBs (category C or D). These all require special consideration in these women.

FMD screening

The prevalence of FMD among patients with SCAD was variable between studies[33,72]. In an autopsy study on 18 patients with sudden cardiac death from SCAD, none were found to have FMD[48]. This could be due to the rarity of SCAD causing sudden cardiac death (only 0.3% from the same study), or a low prevalence of FMD. On the other hand, the prevalence of FMD has been reported to be as high as 86%[33]. In the balance of current evidence, FMD screening has been advocated for in all patients with SCAD[7,8]. In a recent systematic review and meta-analysis, FMD was found to be associated with an increased risk of SCAD recurrence (RR, 2.02; 95% CI, 1.03–3.94; $P = 0.0404$)[65]. FMD screening also allows the detection of high-risk vascular malformations which may require close monitoring or

intervention. Non-selective angiography of the renal and iliac arteries can be performed at the same time as invasive coronary angiography; however, this will not visualise intracranial vessels. Full FMD screening can be performed with head to pelvis CT angiography. Magnetic resonance imaging (MRI) angiography can be used instead of CT, dependent on local availability and individual factors, but has lower spatial resolution than CT. Some experts advocated for using MRI of the cerebral and neck arteries to better define aneurysm and webs. The risks of screening, including those of false positive and false negatives, should be discussed with patients. An international consensus document has been published to guide the management of FMD[36].

Cardiac rehabilitation, physical activity and mental health considerations

Strenuous physical activity has been reported to be a trigger of SCAD, likely due to increased shear stress in the coronary artery. This has raised concerns about physical activity in people with SCAD, including during cardiac rehabilitation. However, multiple studies have demonstrated that cardiac rehabilitation in patients with SCAD is both safe and could improve patients' well-being[73–76]. It is recommended that all patients with SCAD following an ACS should be referred to cardiac rehabilitation[7,8]. Current cardiac rehabilitation programs usually cater for older patients with atherosclerotic MI, and may be less suitable for younger patients with SCAD[74,77,78]. SCAD-specific cardiac rehabilitation programs have been reported with encouraging results and should be used if available[73].

Low intensity activities, moderate aerobic exercise, interval training and weight training with low resistance and high repetition have been recommended for people with SCAD[79]. Moderate-intensity activities can be guided by symptoms with graded increase in activity levels. High intensity activities with abrupt movements and/or extreme head positions should be avoided; however, given the lack of robust evidence, case-by-case discussion may be considered.

Psychological disorders, including depression, anxiety, and post-traumatic stress disorder, are highly prevalent among patients with SCAD, especially in the first year after presentation[77,80–82]. The limited understanding of SCAD and the uncertainty about its treatment and prevention could precipitate stress among survivors. In a recent study, anxiety was the most common mental health disorder that developed after a SCAD event[77]. It is possible that these disorders are both a risk factor and a consequence of SCAD[77,83]. Mental health screening in patients with SCAD is recommended[7]. Peer-support group is helpful for people with ACS and such groups have been developed online for SCAD survivors, including by SCAD Alliance, Beat SCAD and SCAD Research Incorporated[84–86].

Genetic screening

Genetic screening of all people with SCAD is generally low yield and therefore not routinely recommended[7,8]. Genetic testing may, however, be considered in patients with where a genetic basis is more likely, such as recurrent SCAD, multivessel SCAD, extra-coronary vascular abnormalities, a family history of SCAD or of hereditary connective tissue disease (particularly in a 1st degree relative)[64,87]. During clinical assessment, signs of connective tissue disease, such as joint hypermobility and skin hyperextensibility (suggestive of Ehler-Danlos syndrome), arachnodactyly and ectopia lentis (suggestive of Marfan syndrome), should be sought. Echocardiography may also help detect valvular abnormalities suggestive of connective tissue disorders. In patients who genetic screening is deemed appropriate, gene panels developed for aortopathy and connective tissue disorders can be considered[88]. As with all genetic screening, adequate counselling for the patient and their family is essential.

Current research and future directions

Until 2015, most of the publications on SCAD were case reports. The development of SCAD registries around the world has allowed significant progress in our understanding of this condition[12,61,66,89]. However, there are still difficulties in analysis of representative people with SCAD globally; limited by the lack of a SCAD-specific item number in the World Health Organisation's international classification of diseases, and most registries coming from Europe and North America[90]. Given the diagnosis is sometimes unclear on coronary angiography, review of angiography with experienced cardiologists as adjudicators in a core laboratory setting is a feature of current SCAD registries(Canadian-SCAD in Canada, SR-SCAD in Spain, the DISCO in France, the G-SCAD in the Gulf countries, and ANZ-SCAD in Australia and New Zealand)[12,17,89,91,92].

No randomised controlled study (RCT) on SCAD has yet been published. The currently enroling BA-SCAD trial, recruiting patients in Spain with a 2 × 2 factorial design, will be the first[93]. Patients will be randomised 1/1 into groups of beta-blockers vs placebo, and short (1 month) vs long (12 months) antiplatelet therapy. The study will provide important data about the efficacy and safety of beta-blockers and anti-platelet therapy in patients with SCAD but will likely lack sufficient sample size to report on MACE and death.

Photon-counting CT is a new detector technology that allows higher spatial resolution compared to current detector technology. Early studies have demonstrated good diagnostic value of CTCA using photon-counting detector[94,95]. Due to the higher resolution, this technology has the potential to improve the diagnosis of SCAD with further studies required. The role of artificial intelligence (AI) in medicine has been evolving. AI models have been developed to interpret coronary angiograms with modest results[96]. With more data, this technology may help in the diagnosis of SCAD in the future.

Conclusion

SCAD is an increasingly recognised cause of ACS. The diagnosis of SCAD can be challenging, and a high level of clinical suspicion in the setting of ACS in a young person or pregnancy-associated ACS, should be combined with multimodality imaging, where required. Large registry studies have allowed advancement in our understanding of the presentation and natural history of SCAD, but RCT data are lacking and urgently needed to provide robust, evidence-based management. Current data suggests that most patients with SCAD can be managed conservatively without intervention and that beta-blockers are associated with a lower risk of recurrence. However, there is still much unknown regarding treatment. Randomised trials are in the process of being developed and performed and are expected to provide more definitive data to guide management of SCAD.

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Author contributions

Q.D.: conceptualization, writing—original draft preparation, visualisation. S.B.: writing—review & editingPP: writing—review & editing. S.F.: writing—review & editing. J.S.: writing—review & editing. S.M.: conceptualization, supervision, writing—review & editing.

Competing interests

The authors declare no competing interests.

Additional information

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Preamble to the next chapter

This chapter summarises the relevant current literature to inform the clinical management of SCAD. Despite a recent increase in research interest in SCAD, many aspects of its clinical care are still poorly understood. The next chapter describes the design of the Australia-New Zealand SCAD Registry study, a multi-centre cohort study on SCAD in the Australasia region. This Registry is among the largest in the world and is expected to provide high-quality data, which would advance our understanding of SCAD and improve patient care. Data from this registry plays a central role in the research papers that constitute the following chapters of this thesis.

CHAPTER 3: THE AUSTRALIA-NEW ZEALAND SPONTANEOUS CORONARY ARTERY DISSECTION (ANZ-SCAD) REGISTRY

Aims

- To describe the design of the ANZ-SCAD Registry study

Preface

Despite its increasing recognition, SCAD remains an uncommon condition with a prevalence of 1-4% of all ACS. As a result, multisite studies are needed to obtain a sufficient sample size to analyse outcomes in patients with SCAD. The ANZ-SCAD Registry study is a large, multicentre cohort study involving 26 study sites across Australia and New Zealand with a mixed (prospective and retrospective) method of recruitment. This study was designed to generate high-quality data to advance our understanding of SCAD. As the diagnosis of SCAD may be challenging, the core laboratory adjudication was an essential feature of this study, which allowed for a higher level of evidence compared to previous studies without this feature.

Introduction

The importance of spontaneous coronary artery dissection (SCAD) as a cause of myocardial infarction has been discussed in Chapter 1. This chapter discusses the design of the Australia-New Zealand Spontaneous Coronary Artery Dissection (ANZ-SCAD) Registry. The ANZ-SCAD Registry is a multi-centre cohort study involving multiple sites across Australia and New Zealand [1]. As SCAD is relatively uncommon (1-4% of all acute coronary syndromes), the multi-centre approach allowed the collection of a high number of patients, thus maximising the strength of statistical analysis. This approach also minimised the risk of bias usually encountered in single-centre studies.

Aims/ Objectives

The ANZ-SCAD Registry study aimed to characterise the clinical characteristics of patients with SCAD and their outcomes during the index admission, at short-term and long-term follow-up.

Study Design

Study type

Multi-centre cohort study with two arms: retrospective and prospective. There were 26 sites across Australia and New Zealand (22 in Australia and 4 in New Zealand). Participating sites mainly were tertiary hospitals, with regional centres also included.

The study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12621000824864). Human research ethics approvals were granted by the Western Sydney Local Health District Human Research Ethics Committee for the Australian sites (2021/ETH00040) and by the Southern Health and Disability Ethics Committee for the New Zealand sites (2021 FULL 11045).

Study population

Patients who were 18 years or over and were diagnosed with ACS from SCAD based on clinical assessment and invasive coronary angiography were recruited to the Registry.

For the retrospective arm, a waiver of consent was obtained in accordance with the requirements of the Australian National Statement on Ethical Conduct in Human Research. The medical records were searched from 2010 to the current date to identify patients who were diagnosed with ACS caused by SCAD. For the prospective arm, patients with a diagnosis of ACS and SCAD were approached at the time of their hospital admission or soon after discharge. Informed consent was obtained for all patients in the prospective arm.

Study sites

Study sites in Australia included: Alfred Hospital, Blacktown Hospital, Box Hill Hospital, Cabrini Hospital, Concord Repatriation General Hospital, Fiona Stanley Hospital, Gosford Hospital, John Hunter Hospital, Liverpool Hospital, Monash Health, Nepean Hospital, Orange Health Service, Peninsula Health, Prince of Wales Hospital, Royal Adelaide Hospital, Royal Darwin Hospital, Royal Melbourne Hospital, Royal North Shore Hospital, Royal Perth Hospital, St Vincent’s Hospital Melbourne, St George Hospital and Westmead Hospital.

Study sites in New Zealand included Christchurch Hospital, Waikato Hospital, Wellington Hospital and Waitemata District Health Board.

Core laboratory adjudication

Once patients had been identified through the recruitment process, de-identified coronary angiograms and other relevant images, such as computed tomography coronary angiograms (CTCA), intravascular ultrasound (IVUS), and optical coherence tomography (OCT), were submitted to CloudStor, a secure online database system managed by the University of Sydney. Images were adjudicated in a core laboratory at the Westmead Applied Research Centre (University of Sydney) by at least two experienced interventional cardiologists, blinded to clinical information, to confirm the diagnosis of SCAD. In cases of equivocal diagnosis, the images were reviewed by a steering committee consisting of five principal investigators to reach a consensus.

My Role in the ANZ SCAD Registry

During my PhD candidacy, I was involved in each step of this registry, participating in the core laboratory adjudication for all patients (n=~600) included in my thesis publications. I attended the steering committee meetings. I recruited the participants at my own site, obtained consent, and entered the data. I oversaw data monitoring and the identification and correction of missing or erroneous data by liaising with the sites to rectify these issues.

Data collection

Data were collected from the medical records for all patients and managed using REDCap electronic data capture tools hosted at the University of Sydney.[2, 3] REDCap (Research Electronic Data Capture) is a secure, web-based software

platform designed to support data capture for research studies, providing audit trails for tracking data manipulation and export procedures.

Data on baseline characteristics include age, sex, height and weight, ethnicity, background medical history, regular medications, and smoking status.

The primary endpoint was the occurrence of a major adverse cardiovascular event (MACE), defined as the composite of death from any cause, recurrent myocardial infarction (including myocardial infarction from SCAD), stroke or transient TIA, heart failure, cardiogenic shock, cardiac arrest, ventricular arrhythmia requiring cardioversion or intravenous antiarrhythmic agents, or repeat or unplanned coronary revascularisation. Secondary endpoints were each component of the primary endpoint, as well as in-hospital SCAD extension or propagation, SCAD recurrence (defined as de novo recurrent spontaneous dissection not involving extension of dissection of the original SCAD lesion, with new myocardial infarction symptoms and cardiac enzyme elevation).

Prospectively recruited patients received online questionnaires at baseline, 30 days, and then yearly for up to five years. Follow-up was performed electronically by email. If patients did not have email or did not respond to emails, a study coordinator would contact the patient via phone for follow-up, with the use of professional interpreters if required. At the 30-day follow-up, patients also received the EQ-5D-3L questionnaire. The EQ-5D-3L is an instrument to assess quality-of-life [4]. It consists of five domains: mobility, personal care, usual activities, pain or discomfort, and anxiety or depression. For each domain, participants can select one of the three levels, from level 1 (no or minimal effect on daily life) to level 3 (severe impact on daily life). The last part of the EQ-5D questionnaire is a visual analogue scale, where participants rate their overall health at the time on a scale of 0, meaning worst health, to 100, meaning best health.

At one- and two-year follow-up, participants also received the Seattle Angina Questionnaire. This is an instrument to assess the burden of angina symptoms. There are three questions about the level of limitation in daily activities, one question about the frequency of chest pain, and two questions about the effect of angina symptoms on the enjoyment of life [5].

For retrospectively recruited patients, follow-up and endpoints were extracted from the medical record at the time of recruitment.

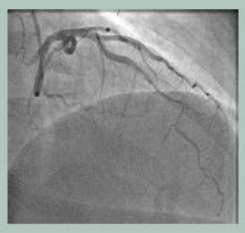
As part of this registry, a clinical protocol guiding the diagnosis and treatment of SCAD was developed and sent to the participating sites (Figure 1). However, this protocol is a guide only, and the management of patients with SCAD remains at the discretion of the clinicians at each of the sites.

Figure 1 – Five-step clinical protocol to guide the diagnosis and treatment of SCAD

5 STEP PROTOCOL FOR OPTIMAL SCAD CARE

Please ensure patient is enrolled in the **ANZ-SCAD registry**.
Contact Study team on _____

STEP 1. CORONARY ANGIOGRAPHY



Coronary angiography is needed to confirm SCAD- urgently if active ischaemia and/or haemodynamic instability. If diagnosis is uncertain, consider **intracoronary nitrates**, intravascular imaging (**IVUS/OCT** *if safe*) and/or **CTCA** to exclude atheroclerosis.

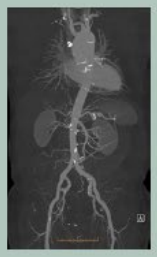
STEP 2. CONSERVATIVE MANAGEMENT

Majority of SCAD will heal over time with conservative management. Consider intervention (PCI/CABG) in the presence of: high risk anatomy (LM/prox 2VD), active ischaemia (not just chest pain), haemodynamic instability

STEP 3. MEDICAL THERAPY

Consider beta-blockers if tolerated, combined with ACEI/ARBs for LV systolic dysfunction. Consider antiplatelets depending on SCAD subtype and intervention (PCI or CABG)

STEP 4. SCREEN FOR FMD



Screen for Fibromuscular dysplasia (FMD) and extra-coronary vascular abnormalities with head-to-pelvis non-invasive angiography by CT or MRI, including intra-cerebral vessels

STEP 5. CARDIAC REHABILITATION

Refer all patients to cardiac rehabilitation and for outpatient cardiologist follow up.
Online SCAD patient support group link:
https://www.facebook.com/groups/AustralianSCADsurvivors/about/

For more information on SCAD please visit: https://www.heartfoundation.org.au/conditions/fp-spontaneous-coronary-artery-dissection

This poster was prepared by the ANZ-SCAD Registry team. ANZ-SCAD Poster_V1_22May2022
This research has been approved by the Western Sydney Local Health District Human Research Ethics Committee

An information leaflet was also developed and distributed to the sites to hand out to patients newly diagnosed with SCAD (**Figure** 2).

Figure 2 – Information leaflet for patients with SCAD

After Discharge from Hospital

Marysia S. Tweet; Physical activity and exercise in patients with SCAD and FMD. Eur Heart J, Volume 42, Issue 37, 1 October 2021

It is also important to know that SCAD can happen again (SCAD recurrence), even many years later. If you develop similar symptoms to the initial episode, such as sudden chest pain, arm/jaw pain, rapid heartbeat, shortness of breath and sweating, then it is important to come to hospital for urgent ECG and blood tests. You may possibly develop different symptoms to your initial SCAD episode. Telling the emergency doctor and nurse that you have had a previous heart attackfrom SCAD would be helpful. Many patients with SCAD don't get a recurrence, however they can experience chronic chest pain or angina.

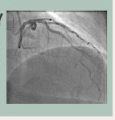
Many people with SCAD also have a rare condition called Fibromuscular Dysplasia (FMD). We recommend a CT scan or other imaging test to look at all the bloods vessels in the body. Your cardiologist can arrange this test.

5 STEP PROTOCOL FOR OPTIMAL SCAD CARE

(Can show to your doctor)

STEP 1. CORONARY ANGIOGRAPHY

Coronary angiography is needed to confirm SCAD diagnosis. If diagnosis is not clear other imaging of arteries maybe performed



STEP 2. CONSERVATIVE MANAGEMENT

Majority of SCAD will heal over time with conservative management. Intervention such as Percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) may be performed if required

STEP 3. MEDICAL THERAPY

Medication such as beta-blockers or ACE inhibitors or ARB inhibitors or antiplatelet treatment will be given if necessary.

STEP 4. SCREEN FOR FMD

Screening for Fibromuscular dysplasia (FMD) and extra-coronary vascular abnormalities is recommended with head-to-pelvis CTor MRI

STEP 5. CARDIAC REHABILITATION

All patients should be referred to cardiac rehab andfor outpatient cardiologist follow up.
Online SCAD patient support group link:
https://www.facebook.com/groups/AustralianSCADsurvivors/about/

Spontaneous Coronary Artery Dissection (SCAD)

Patient Handout

This patient handout was prepared by the ANZ-SCAD Registry team

This research project has been approved by the Western Sydney Local Health District Human Research Ethics Committee. Version 3 dated 23 Jun 2022.

NSW GOVERNMENT Health Western Sydney Local Health District

Overview

Spontaneous coronary artery dissection, or SCAD, is an uncommon condition thatoccurs when a sudden tear or bleed forms in a blood vessel in the heart. SCAD can slow or block blood supply to the heart, whichcan lead to heart attacks and sometimeseven abnormal heart rhythms and death.

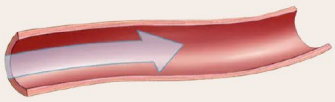
SCAD most commonly affects young and middle-aged women however, it can occurat any age and it can also occur in men. SCAD can affect people who are not typical heart attack patients. Hence it can occur in people who are healthy and fit, lead an active lifestyle, and often have no family history of heart disease. We have astudy registry that collects important information about SCAD and will help usbetter understand how to treat it.

Cause

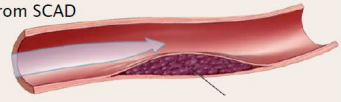
SCAD is NOT caused by traditional risk factors such as high cholesterol, high blood pressure, diabetes, obesity or physical inactivity. This is because SCAD is not related to cholesterol plaque in the heart arteries. Instead, SCAD is believed to be a result ofa sudden tear or bleed or separation of the inner layers of the heart vessel wall.

There are many reasons why this has been thought to occur - such as hormonal changes, including during pregnancy, or sometimes related to extreme stress or physical exercise. However, the exact reasons and underlying genetic risk are yet to be discovered.

a) Blood flow (arrow) through a cross section of a typical artery

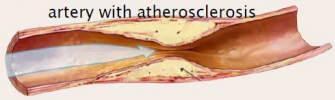


b) Blood flow through a cross section of artery with an intramural haematoma (IMH) from SCAD



Haematoma in SCAD

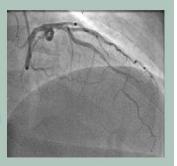
c) Blood flow through a cross section of artery with atherosclerosis



Atherosclerotic plaque (non-SCAD)

In SCAD, a tear forms in an artery in the heart resulting in blood pooling between the layers, called a "hematoma" (b) or "haematoma". As the clot expands it blocks or slows blood flow to the heart. The diagram (c) shows narrowing of the heart artery more commonly due to atherosclerosis, caused by cholesterol plaque deposition.

At the Hospital



A cardiac catheterisation (or coronary angiography) is usually needed to diagnose SCAD. This is when a catheter is placed into an artery in the body up to the heart and used to inject contrast (dye) into the heart arteries.

Most people with SCAD of a heart vessel don't need anything further to open the artery. This is because most SCADs will heal by themselves over the next month. In a small group of people, an emergency procedure such as a stent or bypass surgery, is needed to open the blocked heart artery. If this is done, then blood thinner medications will be needed for up to 12 months.

Most patients with SCAD are treated with blood thinners (such as aspirin and clopidogrel) and beta blockers (such as metoprolol) to prevent further episodes. If you have reduced heart function from a heart attack, you will also be given medications to improve this. Cholesterol tablets, such as statins, may also be needed if you have a reason to take these (such as high cholesterol or diabetes).

Strengths and limitations

The ANZ-SCAD Registry study is the largest study on SCAD in Australia and New Zealand, and a leading cohort globally. The core laboratory adjudication is a key feature and strength of this registry. As the diagnosis of SCAD may be challenging, this ensured that only patients with a clear diagnosis of SCAD were included in the registry, enhancing the reliability of the results. The screening and recruitment of all consecutive patients helped minimise referral bias.

The role of the ANZ-SCAD Registry study in this thesis

The ANZ-SCAD Registry study played a central role in this thesis. It provided high-quality data to allow for the analysis of the incidence of MACE and recurrence in patients with SCAD, and for the analysis of factors independently associated with these endpoints (chapter 4). It also provided data for the study of quality-of-care and its determinants (chapter 6 and chapter 8). Furthermore, the recruitment of prospective patients with SCAD allowed for the analysis of quality-of-life at 30 days. At the time of this thesis's completion, the ANZ-SCAD Registry is still recruiting, and it is expected to generate further high-quality evidence to advance our understanding of SCAD.

Preamble to the next chapter

This chapter describes the design of the ANZ-SCAD Registry and highlights the features that ensure the high quality of the data collected. In the next chapter, data from this Registry were used to analyse the outcomes of patients with SCAD and factors associated with major adverse cardiovascular events and SCAD recurrence.

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15th November 2025

Author contributions statement

This contribution statement is to endorse the role of Quan Minh Dang as the first author and the principal contributor in the preparation and submission of the following manuscript:

Dang QM, Psaltis PJ, Burgess S, Chandrasekhar J, Mukherjee S, Kritharides L, et al. The Australian-New Zealand spontaneous coronary artery dissection cohort study: predictors of major adverse cardiovascular events and recurrence. Eur Heart J. 2025.

During his PhD candidature, Quan Minh Dang was responsible for writing the manuscript, conducting data analysis, and synthesizing the results. As is the nature of peer-reviewed articles, various co-authors made intellectual contributions (roles outlined below). The final published version was primarily due to the efforts of Quan Minh Dang, and by convention, he was named the first author on the manuscript.

Task and Role of Co-Authors

Research question **QD/SZ**	Data curation, synthesis, analysis/ interpretation, visualisation **QD**	Critical revision **All authors**
First draft **QD**	Statistical supervision **SM**	Study supervision **SZ**

Sincerely,

A/Prof Sarah Zaman**,** MBBS, PhD FRACP
Academic Interventional Cardiologist,
Faculty of Medicine and Health and
Westmead Hospital
Primary PhD supervisor

Quan Minh Dang, MD

CHAPTER 4: INCIDENCE OF MAJOR ADVERSE CARDIOVASCULAR EVENTS AND RECURRENCE OF SPONTANEOUS CORONARY ARTERY DISSECTION (SCAD) AND THEIR PREDICTORS

Aims

- To explore the incidence of major adverse cardiovascular events (MACE) and SCAD recurrence in patients from the Australian NZ SCAD Registry and,
- To explore factors associated with MACE and SCAD recurrence

Preface

The ANZ-SCAD Registry is the largest study on SCAD in Australia and New Zealand, and among the largest in the world. In the absence of randomised controlled trials, observational cohorts like the ANZ-SCAD Registry provide the best level of evidence on SCAD. This important paper, published in the leading cardiovascular medicine journal (European Heart Journal), has already been cited in clinical practice guidelines (2025 Australian ACS guidelines), and findings from this chapter may potentially change the way we care for people with SCAD.

ESC European Society of Cardiology

European Heart Journal (2025) **46**, 2012–2023
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]

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See the editorial comment for this article 'The Australian–New Zealand SCAD observational cohort study: major adverse cardiovascular events are associated with ticagrelor combined with aspirin, FMD, and history of stroke', by M.S. Tweet and J.C. Kovacic, https://doi.org/10.1093/eurheartj/ehaf127.

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.

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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

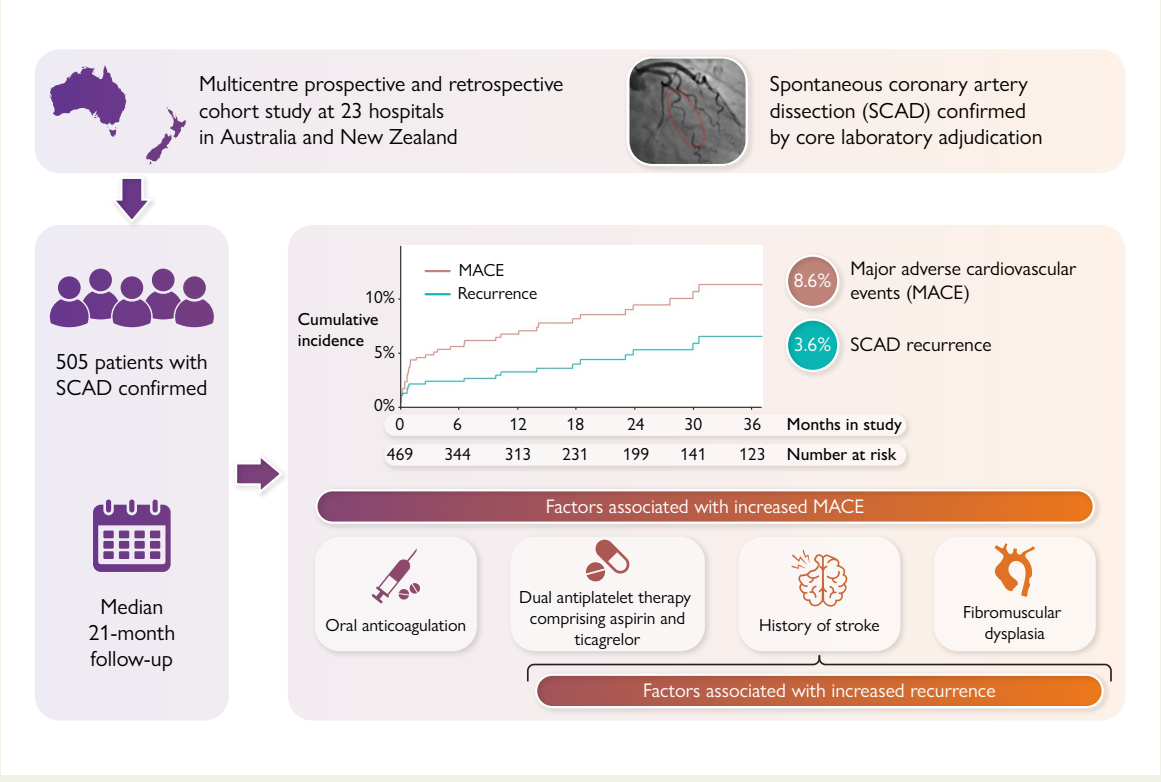
What are the clinical characteristics of patients with spontaneous coronary artery dissection (SCAD) and what are the factors associated with increased risk of major adverse cardiovascular events (MACE) and SCAD recurrence?

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.

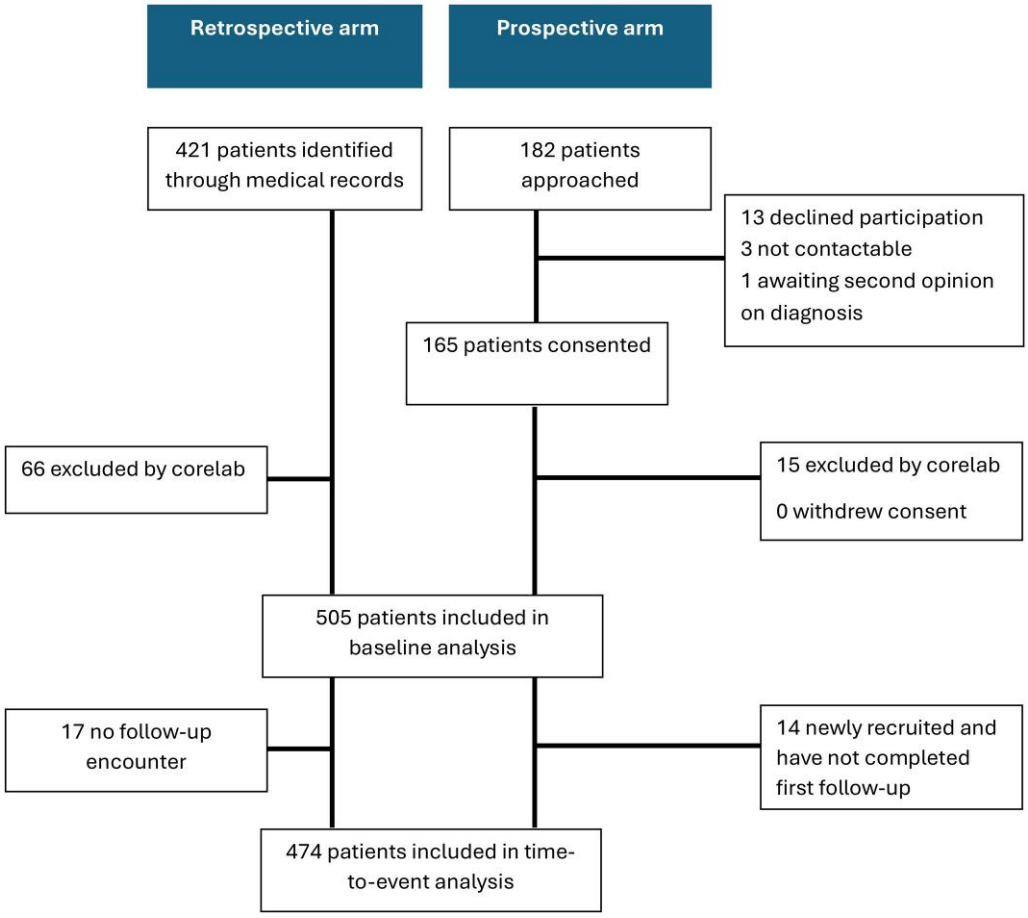


Figure 1 Flow chart of the study

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.

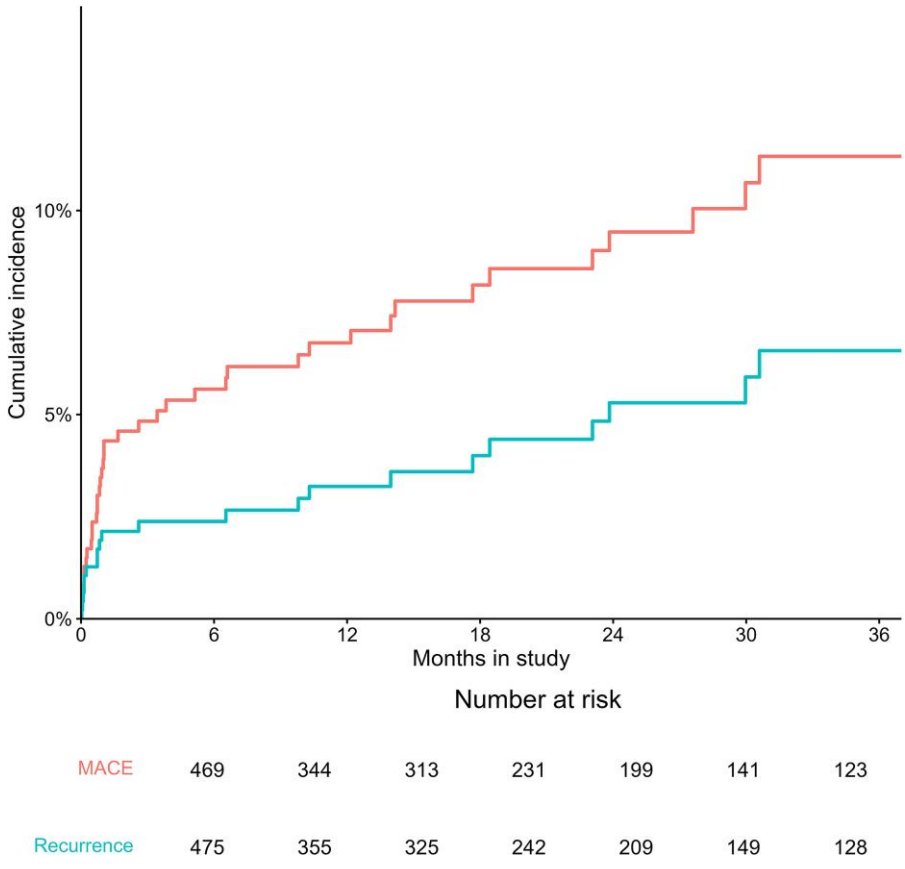


Figure 2 Cumulative incidence of major adverse cardiovascular events and recurrence in people with spontaneous coronary artery dissection. Major adverse cardiovascular event, all-cause death, non-fatal myocardial infarction, non-fatal stroke, heart failure, or target vessel revascularization; Recurrence, *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.

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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.

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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.

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Preamble to the next chapter

This chapter explores the outcomes of patients with SCAD and analyses the independent determinants of MACE and SCAD recurrence. The novel findings that oral anticoagulation and DAPT with a more potent antiplatelet combination were associated with increased risk of MACE add to our understanding of SCAD and may have significant clinical implications. In the next chapter, variation in clinical practice across the world and through time is explored.

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Author contributions statement

This contribution statement is to endorse the role of Quan Minh Dang as the first author and the principal contributor in the preparation and submission of the following manuscript:

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Quan Minh Dang, during his PhD candidature, was responsible for writing the manuscript, performing the systematic search, data analysis, and synthesis of results. As is the nature of peer-reviewed articles, various co-authors made intellectual contributions (roles outlined below). The final published version was primarily due to the efforts of Quan Minh Dang, and by convention, he was named the first author on the manuscript.

Task and Role of Co-Authors

Research question **QD/SZ**

Systematic search **QD/FO/BS**

First draft **QD**

Data acquisition, synthesis, analysis/ interpretation **QD/SM**

Critical revision **All authors**

Study supervision **SZ**

Sincerely,

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CHAPTER 5: SYSTEMATIC REVIEW AND META-ANALYSIS OF THE QUALITY-OF-CARE OF SPONTANEOUS CORONARY ARTERY DISSECTION (SCAD)

Aims

- To explore the quality-of-care of patients with SCAD across the world
- To explore changes in practice after versus before the year 2018, the year of publication of the first consensus documents on SCAD

Preface

Clinicians rely on clinical practice guidelines to manage acute coronary syndromes, with many patients with SCAD being treated similarly to atherosclerosis-related ACS, despite different pathological processes. In the year 2018, the European Society of Cardiology and the American Heart Association both published the world's first consensus documents on the management of SCAD. The quality-of-care of patients with SCAD could then be measured as the level of adherence to these consensus recommendations.

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Regional and temporal variations of spontaneous coronary artery dissection care according to consensus recommendations: a systematic review and meta-analysis

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ABSTRACT

Aim The first expert consensus documents on management of patients with spontaneous coronary artery dissection (SCAD) were published in 2018. Worldwide quality of care, as measured by adherence to these recommendations, has not been systematically reviewed. We aim to review the proportion of patients with SCAD receiving consensus recommendations globally, regionally and, determine differences in practice before and after 2018.

Methods and results A systematic review was performed by searching four main databases (Medline, Embase, SCOPUS, CINAHL) from their inception to 16 June 2022. Studies were selected if they included patients with SCAD and reported at least one of the consensus document recommendations. 53 studies, n=8456 patients (mean 50.1 years, 90.6% female) were included. On random effects meta-analysis, 92.1% (95% CI 89.3 to 94.8) received at least one antiplatelet, 78.0% (CI 73.5 to 82.4) received beta-blockers, 58.7% (CI 52.3 to 65.1) received ACE inhibitors or aldosterone receptor blockers (ACEIs/ARBs), 54.4% (CI 45.4 to 63.5) were screened for fibromuscular dysplasia (FMD), and 70.2% (CI 60.8 to 79.5) were referred to cardiac rehabilitation. Except for cardiac rehabilitation referral and use of ACEIs/ARBs, there was significant heterogeneity in all other quality-of-care parameters, across geographical regions. No significant difference was observed in adherence to recommendations in studies published before and after 2018, except for lower cardiac rehabilitation referrals after 2018 (test of heterogeneity, p=0.012).

Conclusion There are significant variations globally in the management of patients with SCAD, particularly in FMD screening. Raising awareness about consensus recommendations and further prospective evidence about their effect on outcomes may help improve the quality of care for these patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Consensus documents recommended five main interventions for patients with spontaneous coronary artery dissection (SCAD): (1) at least one antiplatelet agent, (2) beta-blocker, (3) ACE inhibitor or aldosterone receptor blocker for patient with left ventricular systolic dysfunction, (4) screening for fibromuscular dysplasia (FMD) and (5) cardiac rehabilitation.

WHAT THIS STUDY ADDS

⇒ This study provides a systematic review of the current practice in managing patients with SCAD worldwide. It identifies low adherence and likely under-reporting of FMD screening and cardiac rehabilitation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Raising awareness among clinicians about these recommendations may help improve the quality of care for these patients.

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is an important cause of myocardial infarction (MI), especially in young women.[1 2] Once thought to be a rare condition, SCAD has been reported to be the cause of up to 4% of all acute coronary syndrome (ACS)[3] and up to 35% of ACS among women less than 50 years of age.[4 5] Despite its significance, our understanding about this potentially life-threatening condition remains incomplete. No randomised data have been published to guide treatment for SCAD, and clinicians have largely relied on standard ACS guidelines. This was not ideal as these guidelines are for atherosclerotic ACS.[1]

In 2018, the American Heart Association and the European Society of Cardiology published the world-first scientific statements on the management of SCAD.[1 2] The recommendations of these documents were based on data from mostly observational studies and, where no data were available, expert

opinions. Although there are some minor variations with regards to the use of antiplatelets, the consensus recommendations for SCAD treatment are similar and can be summarised as follows: (1) at least one antiplatelet agent, (2) beta-blocker, (3) ACE inhibitor (ACEI) or an angiotensin receptor blocker (ARB) in the presence of left ventricular (LV) systolic dysfunction, (4) referral to cardiac rehabilitation and (5) screening for fibromuscular dysplasia (FMD). So far, there have been no data about the effects of these treatments on major adverse cardiovascular events (MACE). The use of beta-blockers was found to be associated with lower risks of SCAD recurrence in a recent systematic review and meta-analysis.[6] As the use of antiplatelets, beta-blockers, ACEI or ARB, and cardiac rehabilitation was also present in guidelines for atherosclerotic ACS, it is worth highlighting the following differences in SCAD consensus recommendations compared with atherosclerotic ACS guidelines: (1) optimal time for antiplatelet therapy was not defined in SCAD and dual-antiplatelets therapy was only recommended if coronary stents were used, (2) ACEIs or ARBs were only recommended in patients with impaired LV systolic function, (3) statins were not recommended in patients with SCAD, and (4) FMD screening was specific for patients with SCAD only and was not recommended in patients with atherosclerotic ACS.

Since the publication of these consensus recommendations, there has been no evaluation of the international implementation of these recommendations. Current optimal quality of care for patients with SCAD around the world is based on the proportion of patients who receive consensus-recommended treatment. The primary aim of this systematic review was to evaluate the quality of care of patients with SCAD, as measured by adherence to global consensus recommendations. Secondary aims included the time from symptom onset to angiography or revascularisation, comparison of adherence to recommendations between geographic regions and before versus after 2018 (the year when the positional papers were published). In addition, for patients presenting with acute MI (AMI), the time from presentation to angiography or revascularisation is an important marker of quality of care, irrespective of the diagnosis of SCAD. As patients with SCAD are often young and without traditional cardiovascular risk factors,[7] we hypothesised that this time would be longer compared with patients with atherosclerotic MI.

METHOD

This systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[8] Ethics approval was not required as only data from published literature was used. This systematic review was registered with the international prospective register of systematic reviews (PROSPERO), ID number CRD42022363414.

Search strategy

A search strategy was developed with a university librarian and performed using the following databases: Medline, Embase, SCOPUS and CINAHL, from their inception up to 16 June 2022. The search was restricted to literature published in English only and using the following search terms: 'spontaneous coronary artery dissection' and 'spontaneous coronary dissection'. The full search strategy can be viewed in online supplemental table 1.

Study selection

To be included in the systematic review, studies either had to be an original cohort or original case series on consecutive patients diagnosed with SCAD and, report at least one of the quality-of-care parameters: that is, proportion of patients prescribed with antiplatelets, beta-blockers, ACEIs or ARBs (in the presence of LV systolic dysfunction) during index hospital admission or at the time of discharge, the proportion of patients screened for FMD, the proportion of patients referred to cardiac rehabilitation and, the time from symptom onset to coronary angiography or revascularisation (where appropriate). The sample size had to be more than 10 patients. Case reports, reviews including systematic reviews, editorials and comments, studies not in English and grey literature (eg, conference abstracts) were excluded.

Screening and data extraction

Literature screening using Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) was performed by two pairs of investigators (QD-FO and QD-BS) independently, using the inclusion and exclusion criteria as defined above. An investigator (QD) performed data extraction while another coauthor (FO/BS/SZ/RZ) checked for consistency. For each study included the following parameters were extracted: author name, year of publication, country of study, site of study, city of study, study name, study aim, type of ACS, sample size, parent SCAD cohort or registry, mean or median age, proportion of female, study design, data collection time, baseline comorbidities, quality of care parameters (the proportion of patients receiving antiplatelets, beta-blockers, ACEIs/ARBs, cardiac rehabilitation, FMD screening, time to angiogram/revascularisation), in-hospital and follow-up MACE (cardiovascular death, MI and stroke) and median or mean follow-up time. With regards to FMD screening, current guidelines recommended CT angiography or magnetic resonance angiography from brain to pelvis. We defined the parameter of FMD screening as having either complete or partial screening.

Included studies were evaluated independently by two investigators for bias using the Newcastle-Ottawa Scale (NOS), a scoring system to evaluate the quality of

non-randomised studies in meta-analysis. The NOS scores studies in three domains, with higher scores mean higher quality thus lower risk of bias. The three domains of the NOS are: (1) selection, with a maximum of four points, (2) comparability, with a maximum of two points, and (3) exposure, with a maximum of three points. Included studies were classified based on their total NOS score: low risk for total score 7–9, medium risk for total score 4–6 and high risk for total score 0–3.

If there were multiple papers based on the same cohort (or registries) of SCAD patients, to avoid duplication, only the most recent publication and/or with the highest number of patients that reported the quality-of-care parameters was included in the meta-analysis. Although not included in the meta-analysis, multiple papers from the same cohort of patients offered an opportunity to assess how quality-of-care parameters for the same cohort changed with time. These studies were presented and discussed separately. If a study had a quality-of-care criterion as a selection requirement (e.g., a study on patients with SCAD who were screened for FMD), data for that criterion were not collected. At any stage of the screening and data extraction process, disagreements between two investigators were resolved by discussion and consensus, with the involvement of a third investigator (SZ) where required.

Statistical analysis

Descriptive statistics were reported using weighted means and SD. Random effects meta-analysis was used to estimate each quality-of-care parameter, reporting mean percentages and 95% CIs. The differences in these parameters across geographical regions and before and after 2018 were assessed using univariate metaregression. Heterogeneity was analysed using Cochran's Q test, which tests whether the variability in the observed effect sizes is larger than would be expected based on sampling variability alone. All analysis was conducted in R (R Foundation for Statistical Computing, Vienna, Austria), using the rma function in the metafor package.

RESULTS

The PRISMA flow chart is presented in figure 1. In total, 2554 articles were screened, and 398 articles were identified for full-text screening. From these, 325 articles were excluded (figure 1). From the remaining 73 articles, 29

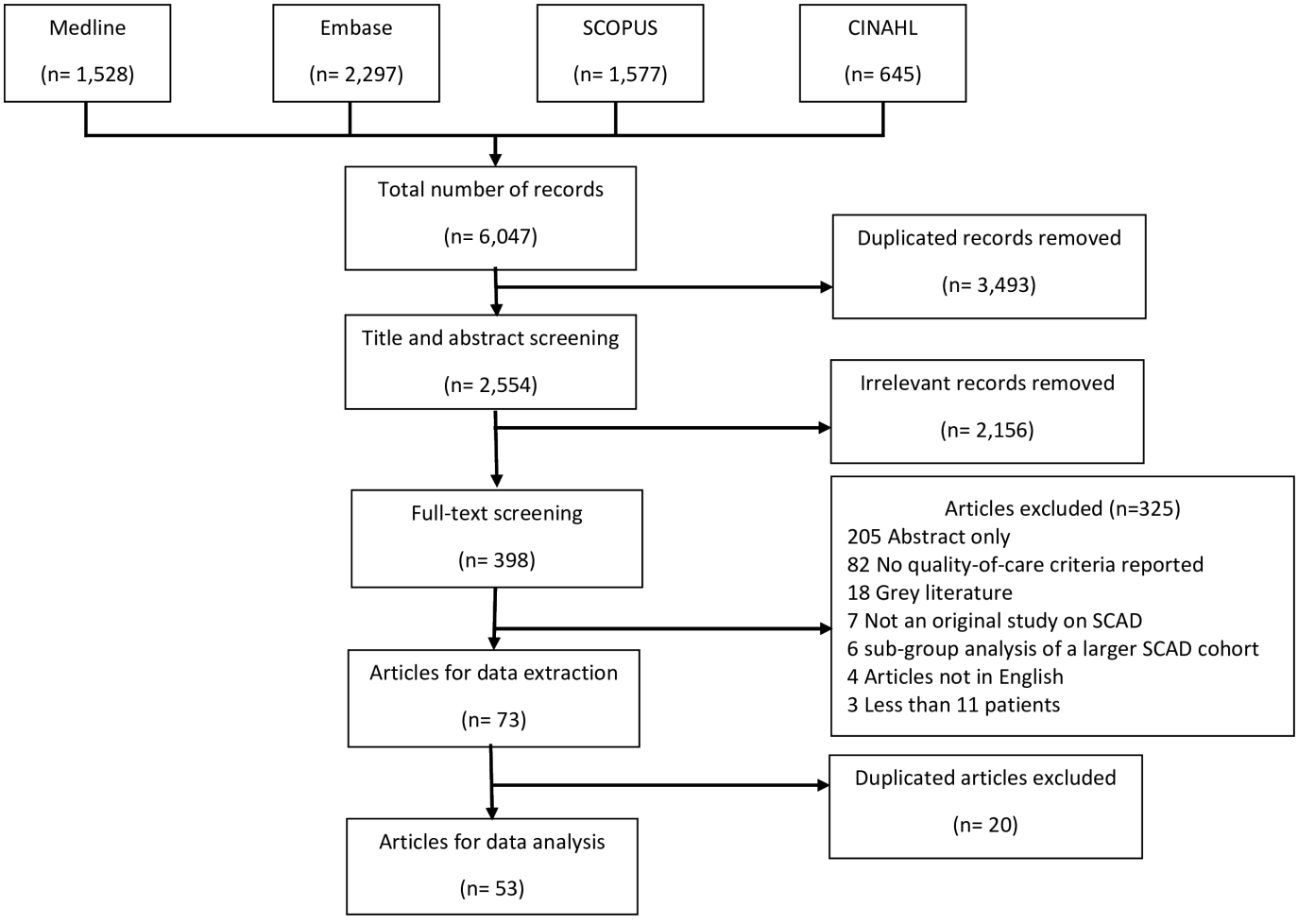

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. SCAD, spontaneous coronary artery dissection.

Table 1 Studies excluded due to data duplication

Potentially duplicated studies	Common cohort	Selected study	Reason of selection
Daoulah *et al*, 2020[16] Daoulah *et al*, 2021[17] Daoulah *et al*, 2021[18] Daoulah *et al*, 2021[19] Daoulah *et al*, 2021[20]	Gulf SCAD Registry	Daoulah *et al*, 2021[20]	Latest study
Saw *et al*, 2014[21] Saw *et al*, 2017[22] Saw *et al*, 2019[23]	Canadian SCAD Registry	Saw *et al*, 2019[23]	Latest study with highest number of patients
Combaret *et al*, 2021[24] Combaret *et al*, 2022[25]	French DISCO Registry	Combaret *et al*, 2021[24]	Highest number of patients (2022 study a subgroup of the registry)
Alfonso *et al*, 2022[26] Diez-Villanueva *et al*, 2021[27] Diez-Villanueva *et al*, 2021[28] Garcia-Guimaraes *et al*, 2021[29] Garcia-Guimaraes *et al*, 2022[30]	Spanish Registry on SCAD	Garcia-Guimaraes *et al*, 2022[30]	Latest study with highest number of patients
Macaya *et al*, 2019[31] Carss *et al*, 2020[32]	UK SCAD Registry	Carss *et al*, 2020[32]	Latest study with highest number of patients
Rogowski *et al*, 2017[33] Seidl *et al*, 2021[34]	Kantonsspital St. Gallen cohort	Seidl *et al*, 2021[34]	Latest study with highest number of patients
Chen *et al*, 2019[35] Chen *et al*, 2021[36]	Kaiser Permanente Northern California cohort	Chen *et al*, 2021[36]	Latest study with highest number of patients
Kok *et al*, 2018[37] Johnson *et al*, 2022[38]	Mayo Clinic Virtual SCAD Registry	Johnson *et al*, 2022[38]	Latest study with highest number of patients
Eleid *et al*, 2014[39] Krittanawong *et al*, 2016[40] Tweet *et al*, 2014[41] Tweet *et al*, 2017[42] Tweet *et al*, 2020[43] Turley *et al*, 2020[44]	Mayo Clinic SCAD Registry	Turley *et al*, 2020[44]	Latest study with highest number of patients

DISCO, DIssezioni Spontanee COronariche; SCAD, spontaneous coronary artery dissection.

were identified to have clear or potential duplicated data from the same cohorts/registries of patients (table 1), with the most appropriate study selected for inclusion. In total, 53 articles, published between 1989 and 2022, were included, with characteristics of the included studies shown in table 2. Overall, n=8456 individuals with SCAD were analysed, mean age 50.1, 90.6% female. Studies were performed in 22 countries which were grouped into 6 geographical regions: Europe, North America, Oceania, East Asia, Middle East and South Asia. Europe had the highest number of studies (20 studies) while North American studies included the highest number of patients (4401). Medical therapy was reported in 39 studies, FMD screening in 24 and cardiac rehabilitation in 3 studies. On assessment of the included studies for risk of bias using NOS, 21 studies were classified as low risk, 28 as medium risk, and 4 as high risk (online supplemental table 2).

Study inclusion and MACE outcomes

Table 3 provides the baseline characteristics of the included studies. Before 2018, there were only 15 studies (n=1065), compared with 39 studies (n=7509) after 2018. The majority of included studies were retrospective (28), followed by prospective (12), cross-sectional (10) and mixed-method (4) studies.

Most studies reported MACE as a composite of death, non-fatal MI and revascularisation with stroke, heart failure, and recurrent or de novo SCAD also reported in some studies. MACE occurred in 7.3% of patients in-hospital and 12.4% on follow-up. Total mortality was reported in 20 studies. Follow-up time varied significantly between studies with mean follow-up ranging between 1 month and 49.2 months.

Time to angiography

Only three studies reported time to angiogram or revascularisation and the methods of report were highly heterogenous. Two studies reported the mean time from symptoms onset to angiogram, with one reported 95% CI (24 hours (4–48))[9] and the other reported standard deviation (7±5.4 days).[10] In another study,[11] door-to-balloon time was reported with the difference between patients with SCAD and other causes of AMI being not statistically significant (median 142 min for SCAD vs 99 min for other AMI, p=0.301). Due to heterogeneity, meta-analysis was not performed for this parameter.

Table 2 Characteristics of included studies

Author	Year	Sample size	Mean or median age	Female percentage	Quality-of-care parameters reported					
					Antiplatelets	Beta-blocker	ACEIs/ARBs	FMD screening	Cardiac rehabilitation	Time to angiogram
Daoulah *et al*[20]	2021	83	44	50.6	98.8	89.2	65.1	0	ND	ND
McGrath-Cadell *et al*[45]	2016	40	45	95	ND	ND	ND	47.5	ND	ND
Rashid *et al*[46]	2016	21	53.3	95.2	100	76.2	80.9	52.4	ND	ND
Adams *et al*[47]	2018	22	48.7	77.3	100	72.7	72.7	ND	ND	ND
Tarr *et al*[48]	2022	91	45.4	91.2	ND	ND	ND	47.3	ND	ND
Chou *et al*[49]	2016	70	52.3	100	95.7	85.7	48.6	ND	ND	ND
Bouchard *et al*[50]	2021	15	47.5	86.7	ND	100	ND	ND	ND	ND
Inohara *et al*[51]	2021	346	53.7	90.2	93.6	86.4	63.6	ND	ND	ND
Solomonica *et al*[52]	2020	16	52.3	93.7	25	25	18.8	ND	ND	ND
Saw *et al*[23]	2019	750	51.8	88.5	93.7	84.8	57.4	73.3	ND	ND
Sun *et al*[53]	2019	85	55	17.6	92.9	68.2	67.1	ND	ND	ND
Hui *et al*[54]	2020	70	50.8	74.3	ND	ND	ND	74.3	ND	ND
Chang *et al*[10]	2022	30	51.8	66.7	90	66.7	76.7	ND	ND	7 days
Mortensen *et al*[55]	2009	22	48.7	81	100	100	ND	ND	ND	ND
Combaret *et al*[24]	2021	373	51.5	90.6	88.3	ND	ND	74.3	ND	ND
Panneerselvam *et al*[56]	2017	64	53.8	6.3	98.4	79.7	81.3	ND	ND	ND
Almasi *et al*[57]	2022	15	48.2	100	92.2	71.4	64.3	ND	ND	ND
Lettieri *et al*[58]	2015	134	52	81	87.3	ND	ND	ND	ND	ND
Antonutti *et al*[59]	2021	70	47	86	100	81	55	ND	ND	ND
Solinas *et al*[60]	2022	58	54	86	100	95	78	31	ND	ND
Cerrato *et al*[61]	2021	199	52.3	88.9	ND	78.9	ND	ND	ND	ND
Nakashima *et al*[5]	2016	63	46	94	ND	ND	ND	39.7	ND	ND
Nishiguchi *et al*[62]	2017	12	63.1	58	100	33	75	ND	ND	ND
Inohara *et al*[63]	2020	322	52.8	100	89.1	62.1	49.4	ND	ND	ND
Inoue *et al*[64]	2021	19	48.7	100	94.7	ND	ND	ND	ND	ND
Kim *et al*[65]	2021	13	52.1	100	53.8	69.2	76.9	ND	ND	ND
McAlister *et al*[66]	2021	113	54	88	99	73	42	ND	ND	ND
Romero-Rodriguez *et al*[67]	2010	19	47.7	79	100	100	100	ND	ND	ND
Alfonso *et al*[9]	2012	17	48	82	ND	ND	ND	ND	ND	1 day
Alfonso *et al*[68]	2012	45	53	58	100	80	53.3	ND	ND	ND

Continued

Table 2 Continued

Author	Year	Sample size	Mean or median age	Female percentage	Quality-of-care parameters reported					
					Antiplatelets	Beta-blocker	ACEIs/ARBs	FMD screening	Cardiac rehabilitation	Time to angiogram
Camacho Freire *et al*[69]	2019	73	55	77	90	ND	ND	ND	ND	ND
Bastante[70]	2020	37	56	97	94	85	64	88	ND	ND
Macaya *et al*[71]	2020	78	53.2	85.9	94.8	80.5	ND	53.8	ND	ND
Mori *et al*[72]	2020	23	52.4	95.7	65.2	69.6	65.2	ND	ND	ND
Garcia-Guimaraes *et al*[30]	2022	389	53	88	93	80	51	27	ND	ND
Murugiah *et al*[11]	2022	67	44.5	92.5	100	83.6	52.2	ND	ND	142 min
Wilander *et al*[73]	2022	147	52.9	75.5	93.1	81.9	59.2	ND	ND	ND
Seidl *et al*[34]	2021	105	53.4	93	97	80	42	38.1	ND	ND
Smaardijk *et al*[74]	2020	172	52	100	ND	ND	ND	75.6	ND	ND
Carss *et al*[82]	2020	384	46.89	94.27	ND	ND	ND	60.4	ND	ND
Androulakis *et al*[75]	2022	144	49	87.5	ND	ND	ND	52.1	ND	ND
Kotecha *et al*[76]	2021	436	ND	93.1	95.2	83	69.7	ND	ND	ND
De Maio Jr *et al*[77]	1989	11	43.1	54.5	36.4	27.3	10.1	ND	ND	ND
Liang *et al*[15]	2014	158	45.2	97	86	62	30	ND	77	ND
Wagers *et al*[14]	2018	367	44.55	100	ND	ND	ND	ND	72	ND
Clare *et al*[78]	2019	208	49	88.9	70.2	83.2	57.2	43.3	ND	ND
Sharma *et al*[79]	2019	113	47	87%	ND	ND	ND	30	ND	ND
McNair *et al*[12]	2020	51	46.9	100	ND	ND	ND	98	ND	ND
Turley *et al*[44]	2020	667	46.7	100	ND	ND	ND	68.1	ND	ND
Chen *et al*[36]	2021	307	49.9	100	94.1	84	59.3	50	ND	ND
Baechler *et al*[13]	2022	115	55	97	88	72	43	41	60	
Johnson *et al*[38]	2022	1196	54	95.6	ND	ND	ND	68.8	ND	ND
White Solaru *et al*[80]	2019	11	47	ND	ND	ND	ND	72.7	ND	ND

ND, no data

Table 3 Baseline statistics of included studies

Total number of patients, n	8456
Mean age	50.1
Female	90.6%
Geographical location, number of studies (n)	
- Europe	21 (2992)
- North America	16 (4401)
- East Asia	8 (614)
- Oceania	5 (287)
- Middle East	2 (98)
- South Asia	1 (64)
Year of publication, number of studies (n)	
- Before 2018	15 (1065)
- After 2018	39 (7509)
Study design, number of studies (n)	
Prospective	12 (2757)
Retrospective	28 (3216)
Cross sectional	10 (1966)
Mixed	4 (635)
Past history, percentage (n)	
Smoking	
- Active	13.0% (4385)
- Past	23.0% (2620)
- Currency status not provided	30.1% (2731)
Hypertension	37.3% (7930)
Diabetes mellitus	4.4% (7945)
Migraine	30.8% (3889)
Peripheral vascular disease	1.5% (298)
Chronic kidney disease	1.9% (994)
History of previous coronary artery disease	8.8% (3077)
Thyroid disorders	13.2% (3122)
Peripartum	10.0% (1522)
Family history of cardiovascular disease	34.6% (2143)
Depression	18.5% (2409)
Anxiety	22.0% (1959)
In-hospital MACE	7.3% (2175)
Follow-up MACE	12.4% (4341)
Range of mean follow-up	1 month–49.2 months
Range of median follow-up	12 months–90 months

MACE, major adverse cardiovascular event; n, total number of patients for whom the data was reported.

Medical management, FMD screening and cardiac rehabilitation referral

Using random effects meta-analysis, 92.1% of patients (95% CI 89.3% to 94.8%) received at least one antiplatelet, 78.0% (95% CI 73.5% to 82.4%) received beta-blockers, 58.7% (95% CI 52.3% to 65.1%) received ACEIs/ARBs, 54.4% (95% CI 45.4% to 63.5%) were screened for FMD and 70.2% (95% CI 60.8% to 79.5%) were referred to cardiac rehabilitation (figure 2). Left ventricular ejection fraction (LVEF) was not reported in most studies. Among the few studies that reported LVEF, none reported if ACEIs/ARBs were given to patients with impaired LVEF. One study[12] reported the proportion of patients (29.6%) who received all consensus-document recommended treatments.

Meta regression analysis of the quality-of-care parameters differed significantly between geographical regions (figure 3) except for the use of ACEIs/ARBs (p=0.088) and cardiac rehabilitation (data for this were only available for North America). Use of at least one antiplatelet was most consistent, with proportions close to 100% in most regions, except for North America (at 78.2%). Use of beta-blockers was also consistently higher than 63% in all regions, while ACEIs/ARBs ranged from 44.2% to 81.3%. Screening for FMD was the most inconsistent parameter, which was lowest in the Middle East (0.6%) and highest in North America (60.5%). North America was also the only region where the rate of cardiac rehabilitation attendance or referral was reported (70.2%, CI 60.9% to 79.5%).

Overall, no significant difference was observed in the proportion of patients receiving each of the recommended treatments between studies published before and after 2018 (figure 4), except for a small deterioration in the proportion of patients undergone cardiac rehabilitation (74.1% vs 60.0%, p=0.012). This parameter, however, was only reported on in North America.

Temporal changes within the same cohorts

The change of quality-of-care parameters within the same cohorts was explored in table 4. Apart from the use of antiplatelets, which consistently increased with time, other parameters fluctuated significantly between the cohorts. The greatest change was observed in the Kantonsspital St. Gallen cohort (drop in FMD screening rate from 62.5% to 38.1%) and Mayo Clinic SCAD Registry (rise in FMD screening rate from 45.5% to 68.1%). There were no data for the change in the rate of referral to cardiac rehabilitation.

DISCUSSION

This systematic review is the first to measure adherence to consensus recommendations in patients with SCAD. Overall, adherence to consensus recommendations in SCAD care was highest for antiplatelet therapy and lowest for FMD screening, with significant variations across geographical regions. There was little change in adherence to consensus recommendations before and after the publication of consensus recommendations in 2018.

Medical management and antiplatelet therapy

The proportions of patients with SCAD receiving antiplatelets, beta-blockers, FMD screening and cardiac rehabilitation were 94.5%, 78%, 54.6% and 70.5%,

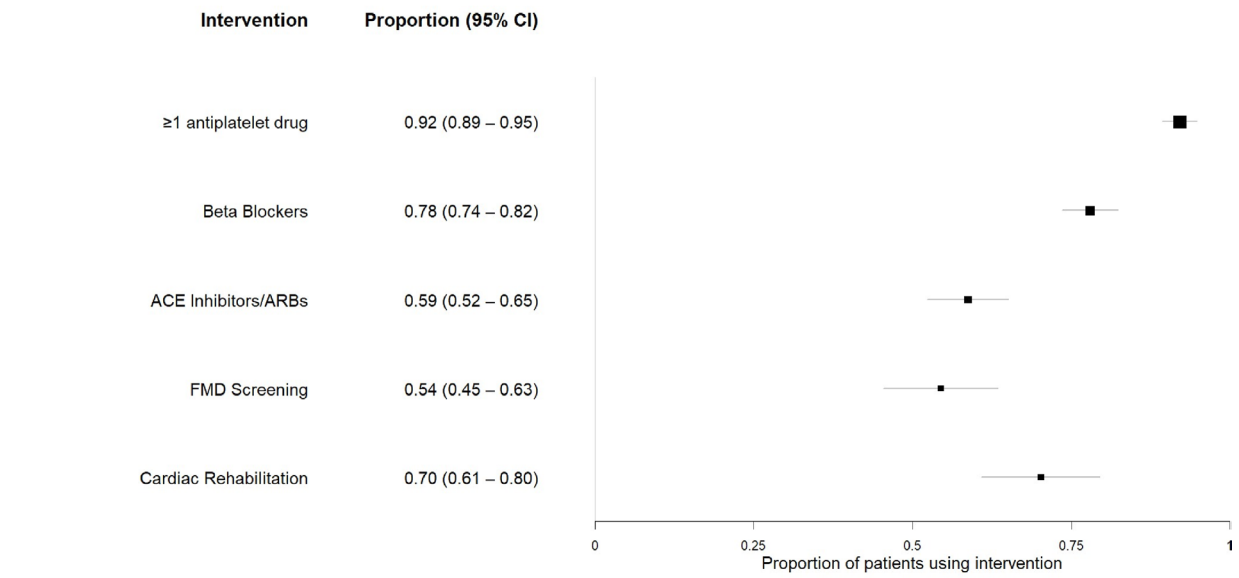

Figure 2 Meta-analysis of quality-of-care parameters—forest plot depiction for random effect meta-analysis of the proportion of patients received each of the recommended interventions using data from all included studies. Note: ARB, angiotensin receptor blocker; FMD, fibromuscular dysplasia.

respectively. With regards to antiplatelet therapy, there is no quality evidence guiding the use of single versus dual antiplatelet, or the duration of therapy. In our review, the proportions of patients on single-antiplatelet therapy were provided in almost all studies which reported on this parameter (35 out of 37 studies), while the use of dual therapy was only provided in half (17 out of 37 studies).

Temporal and geographical trends in SCAD care

No significant change in practice was observed for studies published before and after 2018. The proportion of patients who received all of the recommended treatments would have been a good indicator of overall quality of care. Unfortunately, there was only one paper (Baechler *et al*[13]) that reported this composite parameter,

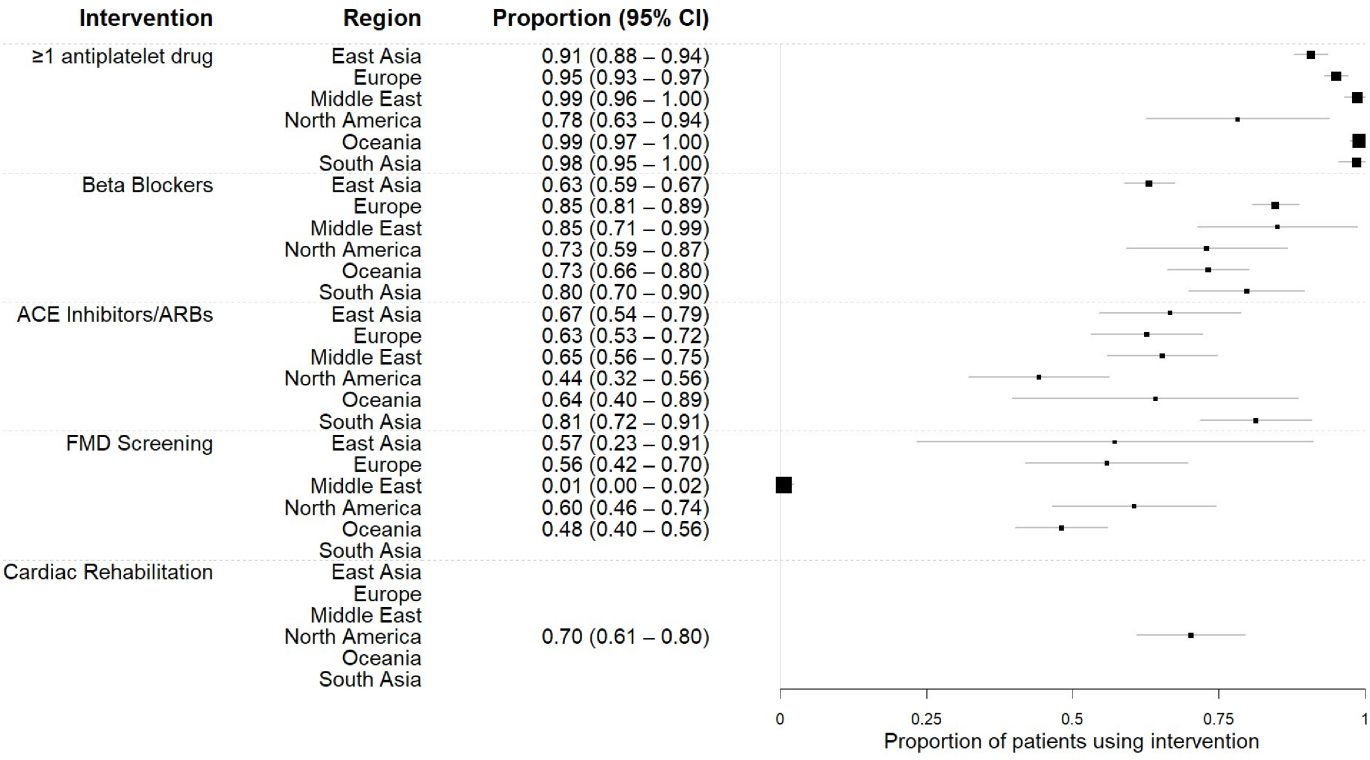

Figure 3 Meta-analysis of quality-of-care parameters by regions—forest plot depiction of random effect meta-analysis of the proportion of patients received each of the recommended interventions, grouped by regions. Note: ARB, angiotensin receptor blocker; FMD, fibromuscular dysplasia.

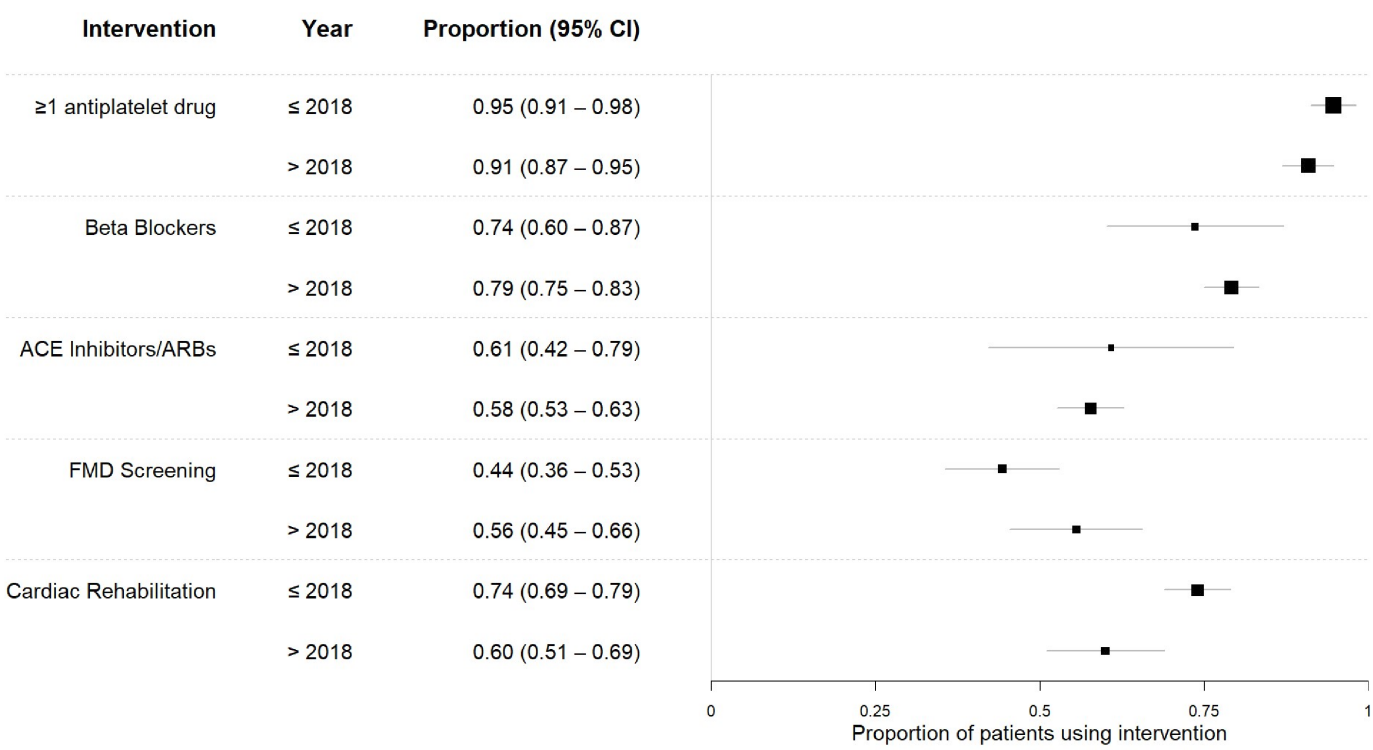

Figure 4 Meta-analysis of quality-of-care parameters by year of publication—forest plot depiction of random effect meta-analysis of the proportion of patients received each of the recommended interventions, grouped by year of publication. Note: ARB, angiotensin receptor blocker; FMD, fibromuscular dysplasia.

with the number relatively low at 29.6%. Notably, there was significant heterogeneity across studies and regions in FMD screening, ranging from 0.6% to 60.6%. This is despite the well-known association between SCAD and FMD, with screening recommended in all patients to look for extracardiac vascular manifestations. Most of the studies included in our systematic review were from higher income countries, highlighting a paucity of data from lower income countries. It is possible that adherence would be lower than our current data, particularly for FMD screening and rehab referral, due to limitations in resources in these countries.

SCAD awareness and cardiac rehabilitation referral

SCAD is an increasingly recognised condition and, consistent with this, we found nearly eight times the number of patients studied in the past 4 years, compared with the 30 years prior. Although there was no significant change in most of the quality-of-care parameters in studies published before and after 2018, this was likely a consequence of later studies including patients recruited historically, diluting any change in the quality-of-care with time. The drop in the proportion of patients who underwent cardiac rehabilitation was related to under reporting and differences in type of reporting. Only 3/53 studies provided information on cardiac rehabilitation, with the method of reporting varied. While one provided the rate of referral to cardiac rehabilitation,[14] the other two reported on the proportion of patients who attended cardiac rehabilitation.[13 15]

LIMITATIONS

This systematic review is limited by the under reporting of several quality-of-care measures, particularly cardiac rehabilitation and FMD screening. We were also unable to determine use of single vs dual antiplatelet therapy in many studies. The benefit of medical therapy in SCAD, such as antiplatelets and beta blockers remains controversial, with no randomised data to support their use. Most studies reported discharge medical therapy whereby adverse effects related to antiplatelets or beta blockers may have led to early cessation, and we cannot comment on adherence to such therapy. The included studies were heterogenous and were conducted with different aims. In a small number of studies, the percentage of females was low, and it is possible that some atherosclerotic dissections may have been included in these studies. There was an under-reporting of the practice of FMD screening (24 studies) and cardiac rehabilitation (three studies). The risk of reporting bias could not be excluded.

CONCLUSION

There are significant variations in the management of SCAD globally, particularly with regards to FMD screening and cardiac rehabilitation referral. An improvement in adherence to recommended therapies is thus needed. Raising awareness among clinicians about these recommendations, together with further prospective evidence on their effectiveness in reducing MACE, may help improve quality of care for patients with SCAD.

Table 4 Change of quality-of-care parameters on the same cohorts with time

Cohort	Study	N	Time from	Time to	Antiplatelets	Beta-blocker	ACEIs/ARBs	FMD screening	Cardiac rehabilitation
Canadian SCAD	Saw *et al*[22] 2017	327	04/2012	12/2016	92	83	57.6	80.7	ND
	Saw *et al*[23] 2019	750	06/2014	06/2018	93.7	84.8	57.4	73.3	ND
Spanish Registry for SCAD	Garcia-Guimaraes *et al*[29] 2021	318	06/2015	04/2019	92	79	51	29	ND
	Garcia-Guimaraes *et al*[30] 2022	389	06/2015	12/2020	93	80	51	27	ND
Kantonsspital St. Gallen cohort	Rogowski *et al*[33] 2017	64	01/1998	01/2015	97	86	36	63	ND
	Seidl *et al*[34] 2021	105	01/1998	12/2020	97	80	42	38.1	ND
Kaiser Permanente Northern California cohort	Chen *et al*[85] 2019	111	01/2003	12/2012	94	88	63	49.5	ND
	Chen *et al*[86] 2021	307	09/2002	06/2017	94.1	84	59.3	50	ND
Mayo Clinic Virtual SCAD Registry	Kok *et al*[87] 2018	585	01/2010	01/2017	89	59	ND	57.3	ND
	Johnson *et al*[88] 2022	1196	08/2011	03/2020	ND	ND	ND	68.8	ND
Mayo Clinic SCAD Registry	Eleid *et al*[89] 2014	246	01/1979	12/2013	ND	ND	ND	45.5	ND
	Turley *et al*[44] 2020	667	08/2011	08/2018	ND	ND	ND	68.1	ND

ND, No data; SCAD, spontaneous coronary artery dissection.

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Preamble to the next chapter

This chapter analyses the quality-of-care of SCAD from an international perspective. It demonstrates significant variations in practice worldwide, with low level of adherence to FMD screening. In the next chapter, the quality-of-care of SCAD from a national perspective is explored.

CHAPTER 6: THE QUALITY-OF-CARE OF PATIENTS WITH SPONTANEOUS CORONARY ARTERY DISSECTION (SCAD) FROM THE AUSTRALIA-NEW ZEALAND SCAD REGISTRY

Aims:

- To assess the quality-of-care of SCAD in Australian and NZ patients by the level of adherence to current consensus recommendations using data from the ANZ-SCAD Registry
- To assess changes in practice over time
- To assess factors associated with adherence to quality-of-care parameters

Preface:

This chapter examined the quality-of-care for patients with SCAD in Australia and New Zealand, as measured by the level of adherence to consensus recommendations. This study follows on from the previous chapter, moving from a global evaluation to local national practice. In addition, data from the ANZ-SCAD registry allowed for in-depth analysis of factors associated with quality-of-care parameters and changes in practice yearly, which were not possible in the systematic review in the last chapter. This paper has been submitted to the Heart, Lung, and Circulation journal (under review) and is presented in its submitted form.

Quality-of-care for Spontaneous Coronary Artery Dissection from the Australian-New Zealand SCAD Registry

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Abstract

Background: Spontaneous Coronary Artery Dissection (SCAD) is an important but underrecognised cause of acute coronary syndrome (ACS). In 2018, the American Heart Association (AHA) and the European Society of Cardiology (ESC) published the first consensus documents that recommended the following for patients with SCAD: at least single antiplatelet therapy, beta-blocker therapy, fibromuscular dysplasia (FMD) screening, and cardiac rehabilitation.

Aims: We aimed to assess adherence to key quality-of-care recommendations for SCAD survivors and changes in practice over time.

Methods: A 23-hospital multi-centre cohort study in Australia and New Zealand from 2010 to 2024 included patients 18 years and older with an ACS and SCAD confirmed on core laboratory adjudication of invasive coronary angiography. Logistic regression analysis with adjustment for age, sex, type of ACS, percutaneous coronary intervention (PCI), left ventricular (LV) function and hypertension was used to assess changes in care over time.

Results: A total of 567 patients with core laboratory-confirmed SCAD were included, mean age 52.0±10.5, 89.1% female, 66.7% non-ST elevation ACS, 33.3% ST elevation ACS and 10.9% received PCI. Overall, 95.4% of patients received at least one antiplatelet agent, 80.8% beta-blocker therapy, 47.8% were screened for FMD, 76.0% were referred to cardiac rehabilitation and 33.3% received all four recommendations. On multivariable logistic regression modelling, the proportion of SCAD survivors who received at least one antiplatelet reduced over time [adjusted odds ratio (aOR) 0.69, 95% confidence interval (CI) 0.51-0.89], beta-blocker therapy was unchanged (aOR 1.08, 95%CI 0.99-1.18) and FMD screening (aOR 1.24, 95%CI 1.13-1.30) and cardiac rehab referral (aOR 1.16, 95%CI 1.07-1.25) significantly increased.

Conclusion: A low proportion of Australian and New Zealand patients with SCAD received all recommended care, with particularly low rates of FMD screening. Significant improvements in

FMD screening and cardiac rehabilitation referral were seen over time, but this did not apply to antiplatelet therapy.

Key words

Spontaneous coronary artery dissection, acute coronary syndrome, quality-of-care, antiplatelet, beta-blocker, fibromuscular dysplasia, cardiac rehabilitation

Introduction

Spontaneous coronary artery dissection (SCAD) is defined as a separation between any two of the three layers of the coronary artery (intima, media, and adventitia) due to a dissection that is spontaneous, not iatrogenic, traumatic, or secondary to atherosclerotic plaque rupture [1]. This may create a false lumen in the coronary artery, with or without communication with the true lumen, and has the potential to obstruct coronary flow, resulting in acute coronary syndrome (ACS) [2]. SCAD is an uncommon cause of ACS, responsible for only 1-5% of overall ACS, however, it is a much more prevalent cause of ACS in young women (up to 35% of cases) and pregnant women (up to 43%) [3-12]. Current guidelines for management of patients with ACS have been developed for atherothrombotic coronary artery disease and may not be appropriate to guide treatment of SCAD, which has a different pathophysiologic mechanism [13-15]. To date, there remains no published randomised controlled trials on SCAD and care of SCAD is based on observational studies and expert opinion. In 2018, the American Heart Association (AHA) and the European Society of Cardiology (ESC) published the first consensus recommendations for the management of SCAD [16, 17] using data available from observational studies. The key management recommendations from these documents for all patients with SCAD included: i) use of at least one antiplatelet agent, ii) use of a beta-blocker, iii) screening for fibromuscular dysplasia (FMD), and iv) referral to cardiac rehabilitation. In the absence of randomised trials studying SCAD management the level of adherence to these key consensus recommendations currently defines best contemporary evidence-based care for patients with SCAD. A recent systematic review and meta-analysis has demonstrated significant variations in the quality-of-care for SCAD worldwide [18]. This study aimed to explore adherence to consensus recommendations in the

management of patients with SCAD in an Australian and New Zealand population, using the Australian New Zealand (ANZ)-SCAD registry and, to compare changes in management of SCAD over time.

Material and methods

Study design

The ANZ-SCAD Registry is a multi-centre, prospective and retrospective cohort study recruiting patients from 23 hospitals across Australia and New Zealand. The study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12621000824864). Multi-site ethics approval was granted for the Australian sites by the Western Sydney Local Health District Human Research Ethics Committee (2021/ETH00040) and in New Zealand by the Southern Health and Disability Ethics Committee (2021 FULL 11045). The protocol for this study has been published separately [19].

Patients of 18 years or over who were diagnosed with SCAD and an ACS were eligible for inclusion. Informed consent was obtained for all patients recruited prospectively while a waiver of consent was applied for those recruited retrospectively in accordance with the Australian National Statement on Ethical Conduct in Human Research [20]. Retrospective patients were identified by screening of medical records back to 2010. Prospective patients were approached by the study team, while an inpatient or soon after discharge, to give their informed consent. All patients had their invasive coronary angiogram and adjunctive imaging performed [e.g. intravascular imaging, computed tomography coronary angiography (CTCA)] and reviewed in the core laboratory, comprising experienced cardiologists blinded to the clinical data. Diagnostically

ambiguous cases were taken to steering committee review, comprising 5-7 principal investigator interventional cardiologists, with majority consensus used for final adjudication. Only patients with SCAD confirmed by core laboratory adjudication were included in the registry. Key parameters used to assess quality-of-care were whether patients were: i) on at least one antiplatelet, ii) on a beta-blocker, iii) screened for FMD, and (iv) referred to cardiac rehabilitation.

Data collection and data management

Retrospectively recruited patients had data extracted from existing medical records. Extracted data included demographics, past medical history and medications on admission, clinical presentation, in-hospital investigations and treatments, in-hospital progress including morbidity and mortality, discharge medications, discharge plans and further adverse events following the index event. Prospectively recruited patients had data extracted from the medical records, in addition to online surveys at baseline, 30 days, then yearly for up to five years. Data was anonymized and managed by REDCapTM, a secure, web-based software platform, also used to deliver online surveys, hosted by the University of Sydney.

Statistical analysis

Statistical analysis was performed as per the prespecified statistical analysis plan. Mean and standard deviation, or median and interquartile range (IQR), were used to summarize continuous variables while count and proportions were used for categorical variables. Univariable and multivariable logistic regression models were used to analyze the change in key quality-of-care parameters with time. Multivariable models were adjusted for age, sex, past history of hypertension, ACS type (ST elevation myocardial infarction [STEMI] versus non-ST elevation acute coronary syndrome

[NSTE-ACS]), the presence of moderate to severe left ventricular dysfunction (defined as left ventricular ejection fraction ≤40%), and use of percutaneous coronary intervention (PCI). A two-tailed p value of 0.05 was considered statistically significant and due to the exploratory nature of the analysis no multiple comparison adjustments were made. Statistical analyses were performed using R-Studio statistical software version 4.4.2. R Core Team, particularly the tidyverse and skimr packages [21].

Results

A total of 567 patients with SCAD diagnosis confirmed on core laboratory adjudication were included (187 prospective and 380 retrospective). The index SCAD event was from 2010 to 2024. The mean age was 52.0±10.5 years, 89.1% (505/567) were female and 73.5% (417/567) Caucasian. The majority of patients had no traditional cardiovascular risk factors, but among those who did have a history of risk factors, hypertension was the most common (29.1%), followed by a family history of premature coronary artery disease (22.8%), and dyslipidaemia (22.0%).The majority of patients presented with NSTE-ACS at 67.2% (381/567) with 32.8% (186/567) presenting with STE-ACS. Overall, the proportion of patients with a left ventricular ejection fraction (LVEF)≤40% was 10.1% (53/523) with an LVEF assessed during the index hospital admission in 92.2% (523/567). Baseline characteristics of patients are summarised in Table 1.

Table 1 – Baseline characteristics of patients with SCAD – n=567

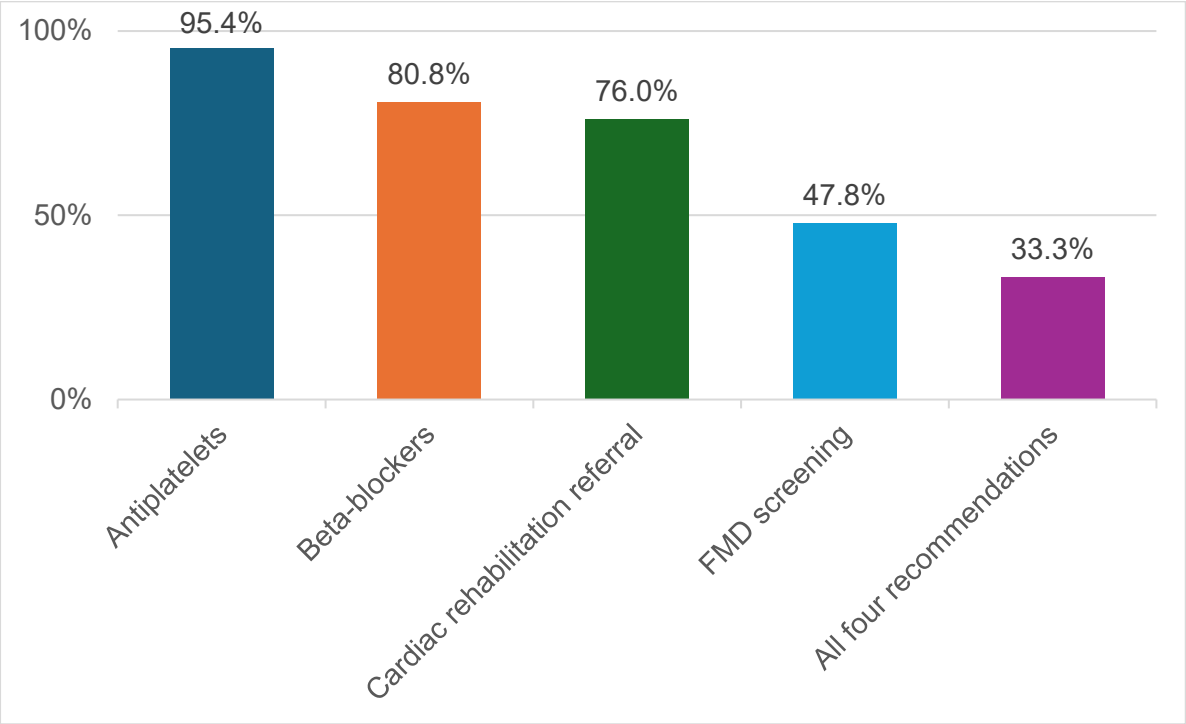
Characteristics	Number (%)
Age at SCAD diagnosis, mean±SD	51.9±10.5
Female sex	505 (89.0%)
Body Mass Index, mean±SD	28.3±6.6
Ethnicity	
• Caucasian	417 (73.5%)
• East Asian	20 (3.5%)
• South Asian	10 (1.8%)
• Aboriginal & Torres Strait Islander	5 (0.9%)
• African	9 (1.6%)
• Maori	22 (3.9%)
• Pacific People	8 (1.4%)
• Middle Eastern and Northern Africa	14 (2.5%)
• Other/ Unknown	75 (13.23%)
Background medical history	
• Family history of premature CAD	129 (22.8%)
• Hypertension	165 (29.1%)
• Diabetes	14 (2.5%)
• Dyslipidaemia	125 (22.0%)
• Stroke/ TIA	7 (1.2%)
• Fibromuscular dysplasia	4 (0.7%)
• Depression	77 (13.6%)
• Anxiety	61 (10.8%)
Current or ex-smoker	33.4%

Type of ACS • ST elevation myocardial infarction • NSTEMI or unstable angina	 186 (33.3%) 381 (66.7)
Percutaneous coronary intervention performed	62 (10.9%)
Left ventricular systolic ejection fraction assessed, of those assessed: Left ventricular systolic ejection fraction ≤40%	523 (92.2%) 53 (10.1%)

CAD: coronary artery disease, SCAD: spontaneous coronary artery dissection, TIA: transient ischaemic attack,

At the time of hospital discharge, the majority of patients received at least one antiplatelet agent (541/567; 95.4%) and a beta blocker (458/567; 80.8%). Most patients were referred to cardiac rehabilitation (431/567, 76.0%). FMD screening, either during the index hospital admission or after discharge, was performed in less than half of patients (271/567; 47.8%). A total of 189/567 (33.3%) patients received all four key recommendations. The proportions of patients who received each quality-of-care parameter are shown in Figure 1.

Figure 1 – The proportion of patients with SCAD from the Australian and New Zealand Registry who received recommended care



On univariable logistic regression model (Table 2), the odds of patients receiving all four key care recommendations increased over time by 19% per year; odds ratio (OR) 1.19, 95% confidence interval [95%CI 1.11-1.27], with the changes across time shown in Supplementary figure 1. In the adjusted models, the estimate of the odds of patients receiving all four key consensus recommendations showed an increase of 23% per year (Table 3), (adjusted (a)OR 1.23, 95%CI 1.13-1.33). The use of at least one antiplatelet significantly decreased each year by 31% (aOR 0.69, 95%CI 0.51-0.89), there was no evidence of a change in beta-blocker use over time (aOR 1.08, 95% 0.99-1.18), while the odds of FMD screening significantly increased by 24% per year (aOR 1.24, 95%CI 1.13-1.30) and cardiac rehabilitation referral significantly increased by 16% per year (aOR 1.16, 95%CI 1.07-1.25). The proportion of patients who received each recommendation according to year of treatment are shown in Supplemental Figures 2-5. The proportion of patients who received at least one

antiplatelet according to year is shown in Supplemental Figure 2. This demonstrated a high use of at least one antiplatelet therapy of 94% - 100% of patients each year, with one low outlier of 86.5% in the year 2023.

Table 2 - Univariable logistic regression model of time and key quality-of-care parameters

Parameters	**Odds ratio (95% confidence interval)**	**P value**
At least one antiplatelet on discharge	0.78 (0.63 – 0.94)	0.01
Beta-blocker on discharge	1.06 (0.99 – 1.14)	0.08
Cardiac rehabilitation referral	1.18 (1.10 – 1.26)	< 0.001
Fibromuscular dysplasia screening	1.19 (1.12 – 1.27)	< 0.001
All four key recommendations	1.19 (1.11 – 1.27)	< 0.001

Table 3 –Multivariable logistic regression model of key quality-of care parameters

Predictor variables	Antiplatelet	Beta-blocker	FMD screening	Cardiac rehab	All four parameters
Time	0.69* (0.51-0.89)	1.08 (0.99-1.18)	1.24* (1.13-1.30)	1.16* (1.07-1.25)	1.23* (1.13-1.33)
Increasing age (per year)	0.94* (0.89-0.99)	0.99 (0.97-1.01)	0.97* (0.95-0.99)	1.01 (0.99-1.03)	0.98* (0.96-0.99)
Female sex	0.79 (0.20-5.3)	0.89 (0.45-1.89)	0.61 (0.34-1.09)	0.82 (0.44-1.59)	0.72 (0.38-1.30)
History of hypertension	1.01 (0.36-3.03)	1.08 (0.64-1.86)	0.86 (0.57-1.31)	0.85 (0.53-1.37)	0.91 (0.59-1.42)
ACS type (STEMI vs NSTE-ACS)	0.32* (0.11-0.89)	1.29 (0.77-2.21)	1.19 (0.80-1.79)	1.14 (0.72-1.84)	1.29 (0.85-1.95)
Treatment strategy (PCI vs conservative)	1.91 (0.43-13.86)	1.27 (0.58-3.10)	0.85 (0.46-1.57)	1.17 (0.58-2.50)	1.07 (0.56-1.99)
LVEF<=40%	0.87 (0.20-6.09)	0.91 (0.43-2.13)	0.53 (0.27-0.99)	1.03 (0.51-2.19)	0.60 (0.29-1.17)

Numbers reported as adjusted odds ratio and 95% confidence interval; asterisks indicate variable with p value <0.05.

ACEI: angiotensin converting enzyme inhibitor, ACS: acute coronary syndrome, ARB: angiotensin receptor blocker, BMI: body mass index, FMD: fibromuscular dysplasia,

LVEF: left ventricular ejection fraction, NSTE-ACS: Non-ST-elevation acute coronary syndrome, STEMI: ST-elevation acute coronary syndrome.

Younger age (aOR 0.94, 95%CI 0.89-0.99) and NSTE-ACS type (aOR 0.32, 95%CI 0.11-0.89) were both significantly independently associated with the lower use of at least one antiplatelet agent while PCI use did not reach significance (OR 1.91). Older age (aOR1.21, 95%CI 1.13-1.30) and more preserved LVEF>40% (aOR 0.53, 95% 0.27-0.99) were independently associated with higher rates of FMD screening as shown in Table 3.

Discussion

This large, multicenter study is the first to assess adherence to the four key quality-of-care parameters for patients with SCAD in an Australian/New Zealand cohort. Adherence to all four recommendations was low at 33% with evidence of improvement over time. The majority of SCAD survivors received at least one antiplatelet agent and a beta blocker, with antiplatelet therapy use decreasing and beta blocker use being consistent over time. Most patients with SCAD were referred to cardiac rehabilitation and this also significantly improved over time. Most concerning was the low rate of FMD screening, with less than half (48%) of SCAD survivors investigated for FMD although reassuringly, this significantly increased over time.

The proportion of patients with SCAD who receive recommended care has not been widely studied [22]. The current study found that only a third of SCAD survivors received all four recommended care measures, comparable to one other published systematic review of 53 studies from 22 countries, where similarly, only 33% of patients received all care recommendations [18]. This suggests that in both Australasia where

this study was performed, and worldwide, there is a significant gap in the care of patients with SCAD. This systematic review reported adherence to recommendations similar to our current study, with 92% of all patients prescribed at least one antiplatelet agent and 78% a beta blocker. Surprisingly, the current study found that use of at least one antiplatelet agent decreased over time. This was seen after controlling for type of ACS and percutaneous coronary intervention (PCI). While this did represent a significant decrease over time, the overall use of at least one antiplatelet agent in the current study remained high at 95%. Further, the decline over time appeared to be influenced by an outlier of low antiplatelet use in the year 2023. As a result, this reduction in the use of at least one antiplatelet therapy in SCAD survivors may not represent a clinically meaningful difference.

Of concern, the current study found that more than half of Australian New Zealand patients with SCAD did not receive FMD screening. Globally, studies have found similar findings, with 46% of SCAD patients not receiving FMD screening in a meta-analysis of 53 studies from 22 countries. However, this under-investigation is not universal, with the Canadian SCAD registry reporting a high proportion of patients screened for FMD of 77% [18, 23]. The importance of FMD screening has been illustrated in past research. In patients with SCAD who were referred for FMD screening, a high rate of FMD has been detected at up to 86% [24-27]. Even in cases where FMD has not been detected, screening also has the potential to uncover non-FMD extra-coronary vascular abnormalities, such as intracranial aneurysms, that may be high risk for rupture, requiring early intervention or close surveillance [1, 28]. The detection of FMD also has important prognostic implications for SCAD survivors. Past studies have shown that patients with SCAD and FMD have a significantly higher risk of major adverse cardiovascular events and SCAD recurrence [23, 27]. The reasons

for low rates of FMD screening in the current cohort were not clear. Hypotheses include a possible low awareness among clinicians of the need for FMD screening or concerns regarding radiation exposure particularly in younger female patients. Whilst the observed improvement in FMD screening over time is encouraging, a substantial gap in guideline-recommended care remains.

The rate of cardiac rehabilitation referral in the current study was reasonable, at 76%, comparable to that of the contemporary atherosclerotic ACS population in Australia, and, significantly improving over time [29-32]. Compared to patients with atherosclerotic ACS, people with SCAD are generally younger, more likely to be female and physically active. Therefore, current cardiac rehabilitation programs which are typically tailored for the older patient with atherosclerotic ACS may not suit SCAD survivors and be a barrier to participation [33]. Education sessions also focus primarily on atherosclerotic ACS and its risk factors, without content specifically for SCAD care. This may lead to under-engagement of patients with SCAD [34]. While a reasonable proportion of patients were referred to cardiac rehabilitation in the current study, rates of participation and completion were not collected. Cardiac rehabilitation programs dedicated to patients with SCAD have been reported with encouraging results however, these programs are not widely available in Australia and New Zealand [35]. Further studies looking at dedicated cardiac rehabilitation programs and SCAD-specific exercise guidance are needed.

Limitations

Although this study was observational in nature, it enabled the analysis of real-world practice in patients with SCAD. While two regional centres were included, most participating sites were tertiary hospitals in Australia and New Zealand which may limit generalisability to clinical practice in other centres and settings. While baseline

variables were adjusted for, when analysing associations with adherence to consensus recommendations over time, unknown or unmeasured confounders may have influenced the outcome. Only discharge medications were analysed and therefore, this study cannot comment on the continued adherence to medical therapy over time. While referral to cardiac rehabilitation was measured, we did not routinely collect cardiac rehabilitation attendance or completion.

Conclusions

In this large Australian and New Zealand cohort study, most patients with SCAD received treatment with antiplatelet and beta-blocker therapy on discharge and were referred to cardiac rehabilitation, consistent with consensus recommendations. However, screening for FMD remained low, despite improvement over time, representing a significant care gap for patients with SCAD.

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Data statement

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

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Author Contributions

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SF: Investigation; Writing - review & editing

AI: Investigation; Writing - review & editing

JL: Investigation; Writing - review & editing

RZ: Investigation; Writing - review & editing

SEJ: Investigation; Writing - review & editing

NP: Investigation; Writing - review & editing

ED: Investigation; Writing - review & editing

IS: Investigation; Writing - review & editing

RA: Investigation; Writing - review & editing

MW: Investigation; Writing - review & editing

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EWL: Investigation; Writing - review & editing

RB: Investigation; Writing - review & editing

TF: Investigation; Writing - review & editing

SL: Investigation; Writing - review & editing

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SZ: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing - review & editing

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Preamble to the next chapter

The previous two chapters explore the quality-of-care of SCAD on the global and national levels. They demonstrate a low level of adherence to FMD screening on both the international and national scales. In the next chapter, the quality-of-care of SCAD from the patient's perspective and its correlation with quality-of-life is investigated.

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Author contributions statement

This contribution statement is to endorse the role of Quan Minh Dang as the first author and the principal contributor in the preparation and submission of the following manuscript:

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During his PhD candidature, Quan Minh Dang was responsible for writing the manuscript, conducting data analysis, and synthesizing the results. As is the nature of peer-reviewed articles, various co-authors made intellectual contributions (roles outlined below). The final published version was primarily due to the efforts of Quan Minh Dang, and by convention, he was named the first author on the manuscript.

Task and Role of Co-Authors

Research question **QD/SZ**	Data curation, synthesis, analysis/ interpretation, visualisation **QD/SM**	Critical revision **All authors**
First draft **QD**		Study supervision **SZ**

Sincerely,

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CHAPTER 7: THE QUALITY-OF-CARE AND ITS CORRELATION WITH QUALITY-OF-LIFE IN PATIENTS WITH SPONTANEOUS CORONARY ARTERY DISSECTION (SCAD) – AN ONLINE SURVEY

Aims:

- To assess SCAD's survivors' perceptions of their quality-of-care, their quality-of-life, and their correlation

Preface:

The previous chapter explored the quality-of-care in a quantitative method, through adherence to consensus recommendations. Quality-of-care could also be assessed qualitatively from the patients' perspective. Prior literature has identified significant issues with patients' experience with clinicians, resulting in considerable anxiety and stress. In this chapter, an online survey was conducted of survivors of SCAD to explore their perceptions of various aspects of their quality-of-care. In addition, long-term quality-of-life was also measured by the EQ-5D questionnaire, which allowed for analysis of the correlation between subjective quality-of-care perceptions and EQ-5D scores.

ESC European Society of Cardiology

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ORIGINAL RESEARCH

Patients' perspective of quality-of-care and its correlation to quality-of-life following spontaneous coronary artery dissection

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Aims Spontaneous coronary artery dissection (SCAD) is an under-recognized cause of myocardial infarction. We aimed to investigate SCAD survivors' perceptions of their quality-of-care and its relationship to quality-of-life.

Methods and results An anonymous survey was distributed online to SCAD survivors involved in Australian SCAD support groups, with 172 (95.3% female, mean age 52.6 ± 9.2 years) participants in the study. The survey involved assessment of quality-of-life using a standardized questionnaire (EQ-5D^{TM}-3L). Respondents rated the quality-of-care received during their hospital admission for SCAD with a median of 8/10 [interquartile range (IQR) 7–10]. Respondents ≤ 50 years vs. >50 years were more likely to perceive that their symptoms were not treated seriously as a myocardial infarction ($\chi^2 = 4.127$, df = 1, $P < 0.05$). Participants rated clinician's knowledge of SCAD with a median of 4/10 (IQR 2–8) and 7/10 (IQR 3–9) for Emergency and Cardiology clinicians, respectively ($P < 0.05$). The internet was the most selected source (45.4%) of useful SCAD information. The mean EQ-5D^{TM} summary index was 0.79 (population norm 0.87). A total of 47.2% of respondents reported a mental health condition diagnosis, with 36% of these diagnosed after their admission with SCAD. Quality-of-life was significantly associated with perceived quality-of-care: EQ-5D^{TM} index/(1-EQ-5D^{TM} index) increased by 13% for each unit increase in quality-of-care after adjusting for age and comorbidities ($P < 0.001$).

Conclusion While SCAD survivors rated their overall hospital care highly, healthcare providers' knowledge of SCAD was perceived to be poor, and the most common source of SCAD information was the internet. Mental health conditions were common, and a significant association was observed between perceived quality-of-care and SCAD survivors' quality-of-life.

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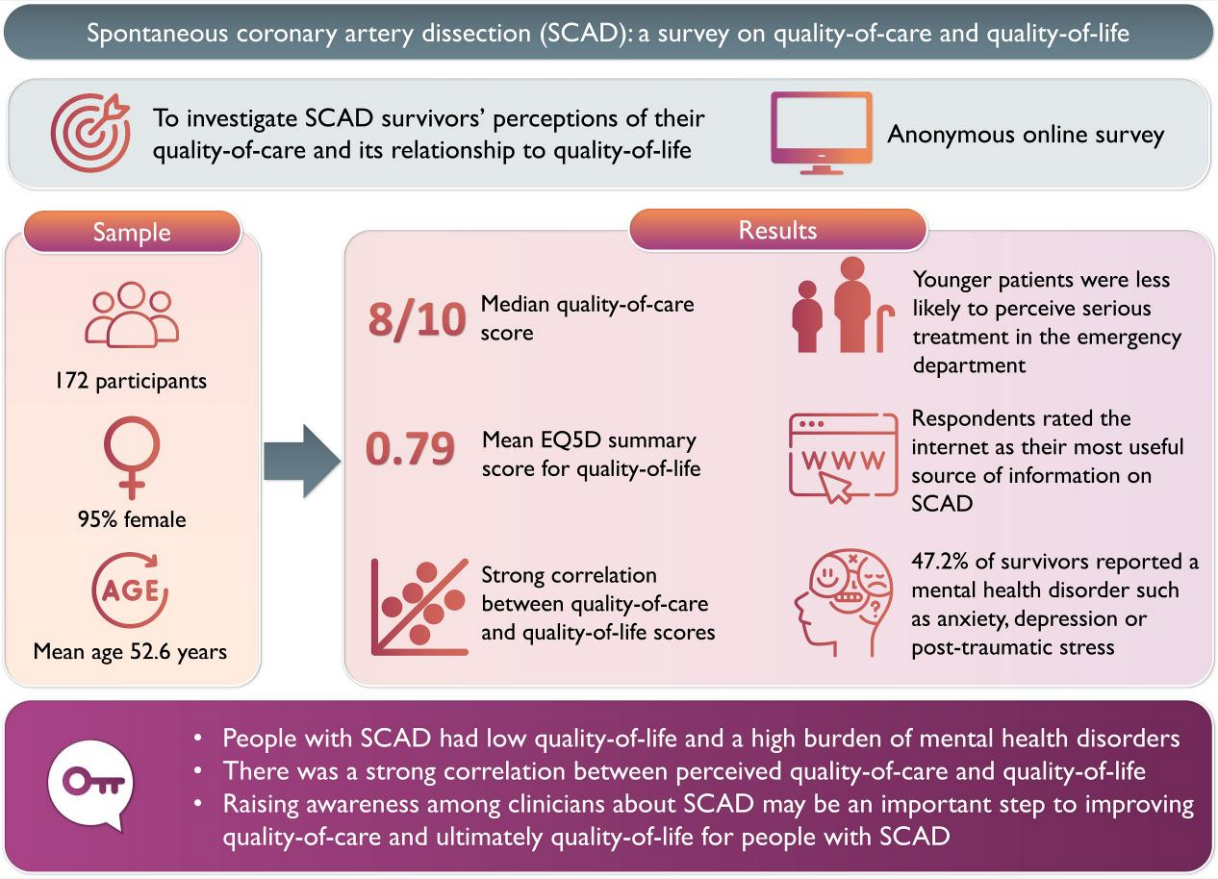
Graphical Abstract



Keywords Quality-of-care • Quality-of-life • Spontaneous coronary artery dissection

Novelty

- There is a deficit in communication between clinicians and spontaneous coronary artery dissection (SCAD) survivors, with a perceived lack of knowledge among clinicians and the internet being the most useful source of information for survivors.
- People with SCAD of younger age were more likely to perceive that their symptoms were taken less seriously in the emergency department.
- Quality-of-life of SCAD survivors was lower than population norm, with high burden of mental health disorders.
- Perceived quality-of-care of SCAD was highly associated with quality-of-life.

Introduction

Spontaneous coronary artery dissection (SCAD) is a cause of acute myocardial infarction, typically affecting younger women without traditional cardiovascular disease (CVD) risk factors. Previously thought to be a rare condition, SCAD is now known to cause 2–4% of acute coronary syndrome, with a strong female (~90%) predominance.[1–4] Our understanding of SCAD is still incomplete. While the first clinical consensus documents to guide the management of SCAD were published in 2018,[5,6] it is likely that many clinicians still have a limited understanding of the disorder. Recent qualitative work has shown that patients with SCAD feel that they receive insufficient and inadequate information from their healthcare providers at the time of diagnosis.[7,8] The internet is more commonly rated as the most helpful information source, than are doctors or other healthcare professionals.[9] This lack of awareness of SCAD in clinicians is likely to contribute to mental distress following SCAD[7,9] and may impair the quality-of-care received. A 2020 survey reported that up to a third of patients with SCAD were not diagnosed at the time of their myocardial infarction (MI).[10]

Spontaneous coronary artery dissection is far from a benign condition, with the rate of in-hospital and long-term major adverse cardiovascular events as high as 10% and 20%, respectively.[11–14] As SCAD predominantly affects young and middle-aged women (median age: 51 years), its impact on survivors' quality-of-life and mental health is likely to be significant. A recent study[15] suggested that younger age was associated with poorer treatment in the emergency department (ED), perhaps related to the perception that younger women are less likely to have MI. Numerous studies have demonstrated high levels

of stress, anxiety, and other mental health challenges during the first year after SCAD.[9,16–18] Indeed, there is evidence that rates of anxiety, depression, and distress may be higher in SCAD survivors than in those with typical atherosclerotic MI.[10,19–21] It is unclear if SCAD is a risk factor for the development of mental health issues, or if mental health issues are risk factors for SCAD, particularly given that stress is commonly cited as a precipitating trigger for SCAD.[5,22–25] No studies have yet investigated the relationship between SCAD onset, the quality-of-care received, and mental health status.

Therefore, the aim of this study was to investigate SCAD survivors' perceptions of their healthcare providers' knowledge of SCAD, the quality-of-care received at the time of their SCAD diagnosis and treatment, and the relationship between these factors and SCAD survivors' quality-of-life and mental health. A secondary aim of the study was to investigate the relationship between SCAD survivors' age and perceptions of the quality-of-care received.

Methods

Study population and recruitment procedure

The study was approved by the Human Research Ethics Committee (HREC) of Western Sydney Local Health District, Australia. Eligible participants were those who had been diagnosed with SCAD and were aged over 18. Eligible individuals were invited to participate in an online anonymous survey, between September and October 2022, which was distributed as follows: (i) posting the details and link to the survey on the Australian SCAD Survivors Facebook group, a private social media group for individuals diagnosed with SCAD, or (ii) emailing SCAD survivors on the email list of SCAD Research Incorporated, an Australia non-government funded charity dedicated to SCAD research and awareness. The social media group consisted of 1100 members, and the email list consisted of 90 email addresses. Therefore, the maximum number of people who were approached to participate in the survey was 1190. The Facebook post and email were repeated twice to increase participant recruitment. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Sydney. Research Electronic Data Capture (REDCap) is a secure, web-based software platform designed to support data capture for research studies. The REDCap database could only be accessed by authorized researchers with password-protected accounts. The database also recorded audit trails for tracking data manipulation and export procedures.

Measures

The survey involved completing an online questionnaire that included a set of demographic questions, namely age, identified gender, place of residence (postcode), and ethnicity (choice of one out of seven options, and one free text option, in case the participant could not choose any of the provided options). Medical information collected included past medical history, number of SCAD episodes, time since most recent SCAD episode, symptoms of SCAD, and time from symptom onset to medical attention. To assess quality-of-care from a patient's perspective, participants rated their overall care (scale of 1—'Incredibly poor care' to 10—'Best care'), time from presentation to consideration of SCAD diagnosis, level of satisfaction with provided SCAD information (five-level Likert scale from 'Completely satisfied' to 'Completely dissatisfied'), most useful source of information (free text), the receipt of treatment for SCAD (antiplatelets, beta-blockers, statins, percutaneous coronary intervention, or coronary bypass surgery), screening for fibromuscular dysplasia (FMD) (Yes/No), referral to cardiac rehabilitation (Yes/No), and cardiologist follow-up (Yes/No). To assess for the seriousness of treatment in the ED, participants rated the statement 'In the Emergency Department, my symptoms were treated seriously as a heart attack (myocardial infarction)' using a five-level Likert scale from strongly disagree to strongly agree. Participants rated the level of knowledge of SCAD of their treating clinicians (e.g. emergency physicians and attending cardiologists) on a scale of 1—'not knowledgeable at all' to 10—'very knowledgeable'. The EuroQol-5 Dimensions-3 Levels (EQ-5D^{TM}-3L) health outcomes instrument was used to assess quality-of-life. The five-item EQ-5D^{TM}-3L has been shown to have good psychometric properties when used with cardiac patients.[26] Participants rated their own health on the EQ-5D^{TM} Visual Analogue Scale (from 0 to 100). An EQ-5D^{TM} summary index (EQ index) was calculated using a formula validated for the Australian population.[27] Chest pain symptoms were assessed using the Seattle angina questionnaire, which has been used previously with SCAD and cardiac patients.[19,28–30] Participants indicated whether they had been diagnosed with a mental health illness, including depression, anxiety, or post-traumatic stress disorder (PTSD) and the timing of this relative to their first episode of SCAD. Finally, participants were asked to make comments (free text) regarding their priority for future research with regards to SCAD. The full survey is shown in Supplementary material online, *File S1*.

Statistical analyses

Findings were reported as counts and frequencies for all variables. Means and standard deviations were calculated and reported for parameters with normal distribution while median and interquartile range were reported for non-normally distributed ones. Chi-square tests were used to assess associations for categorical variables and paired *t*-tests for continuous variables. When assumptions were violated, the Mann–Whitney *U* test was used. The primary objective was assessed using a beta regression with a logit link function and a transformation ([EQ index($N-1$) + 1/2]/N, where N is the sample size) to deal with a EQ index score of 1, adjusting for age and whether the patient had any comorbidities. The data were analysed using IBM SPSS Statistics (Version 29).

Results

A total of 183 questionnaire responses were received, with 11 excluded as responses had been left blank, leaving 172 responses eligible for analysis.

Demographic and clinical characteristics of respondents

Participants' demographic and clinical characteristics are shown in *Table 1*. The median age of participants was 52 years, with a median of 22.0 and 15.5 months having elapsed since the time of their first and most recent SCAD diagnosis, respectively. The majority of participants was female (95.3%) and Caucasian (92.4%). Few respondents had cardiovascular risk factors. A total of 30.2% respondents had a diagnosed mental health condition prior to their SCAD diagnosis, most commonly depression and/or anxiety. Most reported that their SCAD episode was managed conservatively and 61% reported screening for FMD.

Ratings of quality-of-care and clinician's knowledge of spontaneous coronary artery dissection

Parameters related to the quality-of-care of patients with SCAD are provided in *Table 2*. A diagnosis of SCAD was considered on the day of presentation in 57.9% of respondents, and not diagnosed at all during their index admission in 14.5%. Two-thirds (66.3%) of respondents agreed that their symptoms of SCAD were treated seriously as a MI in the ED, and over half (53.5%) were satisfied or completely satisfied with the information about SCAD provided by their doctors. Participants rated their overall care as a median 8 out of 10 (IQR 7–10). Respondents rated their emergency clinicians knowledge of SCAD significantly lower than that of their cardiology clinicians (mean 4.6 vs. 6.4, $t = -6.459$, df = 126, $P < 0.001$). A small proportion (9.4%) of respondents did not attend cardiac rehabilitation despite being referred to it, with the most common barrier to attendance being 'discomfort of being with dissimilar fellow patients (26%)'. Of those who did attend cardiac rehabilitation ($n = 106$), most (78.9%) found that the programme was helpful yet most

Table 1 Demographic and clinical characteristics of respondents

Respondent characteristics	*n* (%)
Age (median in years, interquartile range), *n* = 170	52 (IQR 46–58)
Female, *n* = 172	164 (95.3%)
Ethnicity, *n* = 167	
Caucasian	159 (92.4%)
Aboriginal and/or Torres Strait Islander	4 (2.3%)
Asian	3 (1.7%)
African	1 (0.6%)
Other	5 (2.9%)
Comorbidities and CVD risk factors	
Hypertension	31 (18%)
Hypercholesterolaemia	7 (4.1%)
Diabetes	3 (1.7%)
Cigarette smoking (ever)	35 (20.3%)
Autoimmune/connective tissues disease/FMD	28 (16.3%)
Other	31 (18.0%)
Family history of cardiovascular disease	41 (23.8%)
Mental health diseases prior to SCAD—*n* = 159	48 (30.2%)
Depression	34 (21.4%)
Anxiety	31 (19.5%)
PTSD	11 (6.9%)
Number of SCAD episodes, *n* (%), *n* = 170	
1	132 (77.6)
2	27 (15.9)
3	10 (5.9)
4	1 (0.6)
Time since first SCAD episode (months), median (IQR), *n* = 169	22.0 (5.8–52.0)
Time since most recent SCAD episode (months), median (IQR)	15.5 (4.3–35.8)
Symptoms of SCAD	
Chest pain	119 (69.2%)
Arm pain	79 (45.9%)
Nausea/vomiting	60 (34.9%)
Dizziness	54 (30.8%)
Neck or throat pain	50 (29.1%)
Shortness of breath	45 (26.2%)
Syncope	8 (4.7%)
Time from symptom onset to first medical contact, *n* = 159	
<24 h	141 (88.7%)
>24 h	17 (10.7%)
Uncertain	1 (0.6%)

N = 172.
FMD, fibromuscular dysplasia; SCAD, spontaneous coronary artery dissection; PTSD, post-traumatic stress disorder; CVD, cardiovascular disease; IQR, interquartile range.

(77.4%) were interested in a SCAD-specific cardiac rehabilitation programme. In terms of the most useful source of information about SCAD, almost half (45.4%) the respondents nominated the internet whereas only one in five (19.7%) nominated healthcare providers.

Correlation between quality-of-care and quality-of-life

Quality-of-life was highly associated with perceived quality-of-care [odds ratio (OR) = 1.13, $P < 0.001$] after adjusting for age and patient comorbidities. The interpretation of the beta regression model with a logit link is that the EQ index on the odds scale [EQ index/(1-EQ index)] increased by 13% for each unit increase in perceived quality-of-care. The EQ index increased by 22% for every decade of increasing age (OR = 1.02, $P = 0.022$) and decreased by 31% in the presence of a comorbidity (OR = 0.69, $P = 0.023$).

Respondents' quality-of-life and mental health

Quality-of-life, post-SCAD mental health disorders, and the results of the Seattle angina questionnaire are reported in *Table 3*. The mean EQ-5D^{TM}-3L index score and mean visual analogue scale score were 0.79 and 71.78, respectively. Quality-of-life appeared to be mostly affected in the three domains of usual activities, pain/discomfort, and anxiety/depression, while mobility and self-care were relatively unaffected. A total of 15.7% of respondents reported developing a mental health disorder after their first episode of SCAD, and amongst those who reported this, anxiety (11%) and PTSD (8.7%) were most common.

Association between spontaneous coronary artery dissection survivors' age and ratings of care received

Respondents aged ≤50 were more likely than their older counterparts (aged >50 years) to feel that their MI had not been treated seriously in the ED ($\chi^2 = 4.730$, df = 1, $P = 0.03$). The overall quality-of-care rating was similar for both age groups (mean score 7.4 and 8.1, respectively; Mann–Whitney $U = 3232.5$, $P = 0.24$). Levels of satisfaction with the information on SCAD provided by their doctor did not vary significantly by age (Mann–Whitney $U = 3213.5$, $P = 0.38$) (*Table 4*).

Spontaneous coronary artery dissection survivor's research priorities and concerns

The following research priorities were identified by SCAD survivors, in order of frequency: (i) understanding the underlying reason for SCAD, (ii) improving the quality of medical care for SCAD, (iii) research into the best medical treatments for SCAD, (iv) improving the public awareness of SCAD, and (v) improving understanding of the genetic basis for SCAD.

A total of 133 participants answered the question regarding priority for future research in SCAD using free text. Many also used this free text field to make comments on their experience with SCAD. The overarching theme of these comments was a lack of information, including as follows: (i) a lack of awareness among healthcare providers and the public, (ii) a need for SCAD-specific rehabilitation, and (iii) the mental health and quality-of-life impact of SCAD on survivors. Detailed comments are available in Supplementary material online, *File S2*.

Discussion

This study investigated Australian SCAD survivors' perception of their quality-of-care and their healthcare provider's knowledge of SCAD. While SCAD survivors rated their overall quality-of-care as a median

Table 2 Quality-of-care parameters of patients with spontaneous coronary artery dissection

Respondent characteristics	*n* (%)
Self-reported time from presentation to consideration of SCAD diagnosis—*n* = 159	
<1 day	92 (57.9%)
2–3 days	32 (20.1%)
>3 days	12 (7.5%)
Not diagnosed at index presentation	23 (14.5%)
Overall quality-of-care rating out of 10, mean (SD)—*n* = 156	7.8 (2.4)
Survivor's perception that their symptoms were treated seriously as a heart attack in the emergency department—*n* = 159	
Strongly agree	75 (43.6%)
Agree	39 (22.7%)
Neither agree nor disagree	12 (7%)
Disagree	17 (9.9%)
Strongly disagree	16 (9.3%)
Satisfaction with information about SCAD provided by the doctor—*n* = 159	
Completely satisfied	31 (19.5%)
Satisfied	54 (34%)
Neutral	29 (18.2%)
Dissatisfied	34 (21.4%)
Completely dissatisfied	11 (6.9%)
Clinicians' knowledge of SCAD rating	
Emergency department, median out of 10 (IQR)—*n* = 134	4 (2–8)
Cardiology department, median out of 10 (IQR)—*n* = 147	7 (3–9)
Most useful source for SCAD information	
Internet	60 (45.4%)
Support groups	45 (34.1%)
Healthcare providers	26 (19.7%)
Other	1 (0.8%)
Medical and surgical treatment received for SCAD	
Aspirin	143 (83.1%)
Second antiplatelet agent	100 (58.1%)
Beta-blockers	136 (79.1%)
Statins or other cholesterol reducing agents	93 (54.1%)
ACEI/ARB	5 (2.9%)
Stenting or balloon angioplasty	16 (9.3%)
Coronary artery bypass surgery	4 (2.3%)
Attended cardiologist follow-up after SCAD episode—*n* = 159	
Yes	151 (95%)
No/uncertain	8 (5%)
Awareness that FMD is associated with SCAD—*n* = 160	
Yes	142 (88.8%)
No/uncertain	18 (11.2%)
FMD screening—*n* = 159	
Yes	104 (65.4%)
No/uncertain	55 (34.6%)
FMD diagnosis	
Yes	24/104 (23.1%)
No/uncertain	80/104 (76.9%)
Cardiac rehabilitation referral—*n* = 158	
Yes	119 (75.3%)
No	39 (24.7%)
Cardiac rehabilitation engagement—*n* = 170	
Fully completed programme/still in the programme	88/117 (75.2%)
Attended the programme but did not fully complete	18/117 (15.4%)
Did not attend the programme	11/117 (9.4%)
Cardiac rehabilitation type—*n* = 165	
General cardiac rehabilitation	107/112 (95.5%)
SCAD-specific cardiac rehabilitation	5/112 (4.5%)
Helpfulness of cardiac rehabilitation—*n* = 170	
Helpful	48/104 (46.2%)
Somewhat helpful	34/104 (32.7%)
Neutral	10/104 (9.6%)
Somewhat unhelpful	5/104 (4.8%)
Unhelpful	7/104 (6.7%)
Barriers to cardiac rehabilitation attendance	
Discomfort of being with dissimilar fellow patients	31/119 (26.0%)
Unsuitable rehabilitation programme	19/119 (16.0%)
Lack of time	14/119 (11.8%)
COVID-19-related	11/119 (9.2%)
Rehabilitation centre not being nearby	10/119 (8.4%)
Interest in a SCAD-specific cardiac rehabilitation programme—*n* = 106	
Yes	82 (77.4%)
No/not sure	16 (22.6%)

N = 172.
ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; SCAD, spontaneous coronary artery dissection; FMD, fibromuscular dysplasia; COVID-19, coronavirus disease.

8 out of 10, healthcare provider's knowledge of SCAD was perceived to be poor, and the most common source of information on SCAD was the internet. Pre-existing mental health conditions were common in SCAD survivors, occurring in 30.2%, with a new mental health diagnoses post-SCAD reported in 17%. While the majority of SCAD survivors agreed their symptoms had been treated seriously as a MI, younger patients were significantly less likely than their older counterparts to report this. We found a significant association between SCAD survivors' perceived quality-of-care and their quality-of-life.

We found that SCAD survivors' perception of their treating clinicians' knowledge on SCAD, particularly within the ED, was poor. Two-thirds of respondents reported that their condition had been treated seriously in the ED; findings consistent with a recent study by Stevens *et al.*[15] with 71% of their cohort reporting serious treatment and 10% reporting dismissal treatment. While emergency clinicians

Table 3 Quality-of-life parameters

EQ-5D™ questionnaire	Mobility	Self-care	Usual activities	Pain/discomfort	Anxiety/depression
Level 1, *n* (%)	141 (90%)	154 (98%)	92 (59%)	82 (52%)	77 (49%)
Level 2, *n* (%)	16 (10%)	3 (2%)	62 (39%)	75 (48%)	71 (46%)
Level 3, *n* (%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)	8 (5%)
EQ-5D™ summary index, mean (±SD)			0.79 (±0.16)		
EQ-5D™ visual analogue scale, mean (±SD)			71.78 (±15.6)		
Seattle angina questionnaire					
Physical limitation—*n* = 152			78.9 (±19.9)		
Angina frequency—*n* = 154			84 (±18.3)		
Quality-of-life—*n* = 154			63.4 (±25.7)		
Summary score—*n* = 152			67.7 (±17.2)		
Post-SCAD mental health issues—*n* = 159			27 (17.0%)		
Depression			12 (7.5%)		
Anxiety			19 (11.9%)		
PTSD			15 (9.4%)		

N = 172.
EQ-5D™, EuroQol 5-Dimensions; PTSD, post-traumatic stress disorder; SCAD, spontaneous coronary artery dissection.

Table 4 Association between age and quality-of-care

		≤50 years old	>50 years old	*P* value
Serious treatment received in ED	Agree	41	71	0.03
	Neutral or disagree	25	20	
Overall quality-of-care score, median (IQR)		8 (6.25–10)	8 (7–10)	0.24

N = 157.
IQR, interquartile range; ED, emergency department.

were perceived to be less knowledgeable about SCAD than cardiologists, even the latter received a broad range of scores (1 through to 10/10), showing significant heterogeneity in perceived SCAD knowledge. In a recent qualitative study on the psychosocial impact of SCAD, the lack of information about SCAD, particularly from treating clinicians, was found to be a major issue for SCAD survivors.[7] In a survey reported by Wagers *et al.*[9], SCAD information was rated as inadequate by 82% of largely American respondents. In the current study, we found that 28% of Australian SCAD survivors were not satisfied with the information provided by their treating doctors; the lower response in our study perhaps reflecting an improvement in clinicians' knowledge about SCAD over the 5+ years since the Wagers *et al.*[9] study. Nevertheless, consistent with Wagers *et al.*, the internet remains the most useful source of information about SCAD: our finding that 45% of respondents rated the internet as the most useful information source is only slightly lower than the 52% reported by Wagers *et al.* in 2018. The lack of information provided to patients with SCAD, coupled with low levels of knowledge about SCAD among clinicians, likely worsens the psychological impact of a SCAD event. Our findings highlight the need for education of clinicians about SCAD, particularly emergency clinicians, and improved communication of this knowledge to their patients.

Recent international consensus documents on SCAD[5,6] advocate for antiplatelet and beta-blocker therapy as well as a cardiac rehabilitation referral and FMD screening. In our study, 37% of SCAD survivors reported receiving all of these recommendations, which is slightly higher than the 30% reported in a cohort of SCAD survivors in the USA.[31] Cardiac rehabilitation has been shown to be safe for patients with SCAD and can improve well-being.[32–34] In our study, 75% were referred for cardiac rehabilitation, comparable to previous US studies.[9,16,31,33] Most of the participants in our survey attended a general cardiac rehabilitation programme, rather than a SCAD-specific one. Similar to previous work,[8,33] we found that the main barrier to cardiac rehabilitation attendance was the poor suitability of the programme to SCAD patients, who are usually younger and much more likely to be female than people with atherosclerotic myocardial infarction. The development of SCAD-specific cardiac rehabilitation programmes, therefore, may facilitate participation and play a role in improved well-being of SCAD survivors.

Fibromuscular dysplasia has been well-established to be associated with SCAD, with screening in all patients being advocated.[5,6] In clinical practice however, FMD screening has been inconsistent across the world, ranging from 0% to near 100%.[11,12] In our study, 61% of participants reported being screened for FMD. It is interesting to note that the number of SCAD survivors who reported knowledge of the association of FMD with SCAD was higher than the number referred for FMD screening (142 vs. 104 people). This suggests that participants gained this knowledge by means other than their doctors. This is consistent with the finding that the internet and support groups were the two most common useful sources of information for the participants. Once again, our findings highlight the importance of education of clinicians to improve awareness of SCAD and the need for screening to look for extracardiac manifestations.

Delays to diagnosis with SCAD are an important aspect of medical care. In our survey, just over half of the participants reported a diagnosis of SCAD within 24 h of presentation, while in 14.5%, the

diagnosis was not made during the index presentation. Due to the nature of an online survey, it was not possible to know the exact presentation i.e. MI with or without persistent ST-segment elevation. Without this information, it is difficult to judge whether lengthier times to diagnosis were explicable. Our number of delayed diagnoses is slightly higher than a previous study in the USA, where 10% of patients were discharged from the ED without a diagnosis.[15] We also found that, consistent with past research, younger people with SCAD (≤50 years) identified as being treated less seriously by emergency clinicians, compared to older people. This may reflect clinicians' perception that younger people, particularly in the absence of traditional cardiovascular risk factors, are at low risk for an acute myocardial infarction. Raising awareness of alternate causes of MI, particularly among younger women, may help combat delays in diagnosis and management of SCAD.

The quality-of-life of participants in our survey, at a median of 15.5 months from the most recent SCAD diagnosis, was lower than that of the Australian population, with a mean EQ5D-3L index score of 0.79 [compared to population norm of 0.87[35] ($P < 0.05$)]. Similar to a previous study, quality-of-life of SCAD survivors in our survey was comparable or worse than patients 1 year after atherosclerotic MI (where EQ-5D^{TM} index score was 83.7).[19] However, this comparison is limited by different cohort inclusion, median age, and different lengths in timing from event. In our study, perceived higher quality-of-care was positively correlated with better quality-of-life. Mental health is an important issue for SCAD survivors, with reports of a high prevalence of mental health disorders.[10,16,17,36–38] In a small survey, more than 78% were diagnosed with a mental health condition, and 73% of these patients reported that these conditions were related to the development of SCAD.[17] In our study, 47.2% of participants reported at least one mental health disorder and 36% of these were diagnosed after the first episode of SCAD. It is possible that mental health disorders are both a risk factor for, and a consequence of, SCAD. Therefore, it is important to screen for mental health conditions in patients with SCAD.

The presence of people with SCAD in our current study who identified as being of Aboriginal or Torres Strait Islander background (2.3%) is worth highlighting, as no previous study has reported SCAD in Australian First Nation's peoples. The gap in health outcomes between Aboriginal and Torres Strait Islander Australians and non-Indigenous Australians with cardiovascular disease in Australia has been well described.[39–41] However, the small number of such cases in our study limits any subgroup analyses. The currently recruiting Australian-New Zealand SCAD Registry (ANZ-SCAD)[42] will provide more information on this issue.

Limitations

The study has several limitations that should be taken into account in interpreting the findings. This was an online, anonymous survey, with all data self-reported. The reliance on self-reporting means that the study is limited by a lack of core-laboratory adjudication and diagnosis of SCAD. For some participants with multiple episodes of SCAD, different experiences with the healthcare system may have occurred for each SCAD episode, with participants asked to rate their most recent SCAD admission. The variable length of time between the SCAD episode and completing the survey may itself contribute to the disparities in patients' scoring of their quality-of-care. The response rate was low however, is similar to that of other online surveys of this nature.[43,44] Due to the recruitment of participants from an online support group, selection bias may be present, as individuals with a higher socioeconomic background and/or English as their first language may be more likely to participate, and people actively seeking a support group might be more likely to perceive that there were gaps in their treatment or information received. Mental health issues were addressed by self-report that, once again, cannot be confirmed as physician-diagnosed conditions. Furthermore, individuals with severe mental disorders may have declined completing the survey due to the discomfort raised when recalling events. The EQ5D and SAQ are well validated instruments used in patients with coronary artery disease,[19,28–30,45,46] and their use in SCAD while previously performed[19] has not been extensively studied.

Conclusion

This online survey found that SCAD survivors reported a lack of knowledge and awareness about SCAD in their healthcare providers with quality-of-care significantly associated with quality-of-life. Raising awareness among clinicians about SCAD, including its presentation, diagnosis, and treatment, may be an important step in improving quality-of-care and ultimately quality-of-life in patients with SCAD.

Supplementary material

Supplementary material is available at *European Journal of Cardiovascular Nursing* online.

Author contributions

Q.D.: conceptualization, methodology, investigation, formal analysis, writing—original draft preparation. B.M.: writing—review and editing. R.G.: writing—review and editing. A.P.: writing—review and editing. S.F.: resources, writing—review and editing. S.M.: software, formal analysis, data curation, writing—review and editing. J.C.: writing—review and editing. S.M.: conceptualization, writing—review and editing, supervision.

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Conflict of interest: None declared.

Data availability

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

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Preamble to the next chapter

This chapter investigates the quality-of-life of patients with SCAD on the long-term basis. It demonstrates lower long-term quality-of-life compared to the general population, and a correlation between perceived quality-of-care and quality-of-life. In the next chapter, the short-term effect of SCAD on patients' quality-of-life is explored using the ANZ-SCAD Registry. The Registry's design also allows for the analysis of factors independently associated with quality-of-life.

CHAPTER 8: HEALTH-RELATED QUALITY-OF-LIFE AND ITS DETERMINANTS IN PATIENTS WITH SPONTANEOUS CORONARY ARTERY DISSECTION (SCAD) FROM THE AUSTRALIA-NEW ZEALAND SCAD (ANZ-SCAD) REGISTRY

Aims

- To explore the quality-of-life of patients with SCAD from the ANZ-SCAD Registry using the EQ-5D-3L questionnaire
- To explore factors associated with better or worse quality-of-life

Preface:

The previous chapter assessed quality-of-life of patients with SCAD at a median 22 months following the index event. This chapter assessed the short-term quality-of-life at one month after the index SCAD event, in prospective patients from the ANZ-SCAD registry. Data from the ANZ-SCAD Registry also allowed analysis of factors that were associated with better or worse quality-of-life, forming the basis for future studies to improve the well-being of SCAD survivors. This paper has been submitted to Heart, Lung and Circulation journal (under review), and is presented in its submitted form.

Health-related quality-of-life and its determinants after acute coronary syndrome caused by spontaneous coronary artery dissection

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Abstract

Background

Spontaneous coronary artery dissection (SCAD) is a cause of acute coronary syndrome (ACS) linked with profound impact on mental health and health-related quality-of-life (HRQoL). This study aimed to explore the determinants of HRQoL for patients with SCAD.

Methods

Multi-centre, prospective cohort study in 23 hospitals across Australia and New Zealand. Patients ≥18 years diagnosed with SCAD confirmed on core laboratory adjudication were recruited and gave their informed consent. Health-related quality-of-life was measured using the EQ-5D questionnaire at 30 days after index SCAD event. Beta regression model was used to explore determinants of health-related quality-of-life.

Results

From 2021 to 2025, 193 people with confirmed SCAD were prospectively recruited. Mean age 52.7±10.7 years, 89.1% female, mean body mass index 28.2±6.2 kg/m2, 82.4% Caucasian. At least one cardiovascular risk factor was present in 50.8%, with hypertension the most common (30.1%). At a median of 33 days from the index SCAD event, the mean EQ-5D index summary score was 0.77±0.19 and the mean EQ-5D visual analogue scale (VAS) score was 68.5±17.1. 43.0% had at least moderate pain/discomfort and 57.0% had at least moderate anxiety or depression. On multivariable analysis, fibromuscular dysplasia (FMD, Coefficient -0.25, p=0.005), and female sex (Coefficient -0.35, p=0.04) were independently associated with lower QoL scores.

Conclusions

SCAD has a significant impact on the health-related quality-of-life of survivors with high rates of pain, anxiety and depression. Female sex and an FMD diagnosis were independent predictors of lower health-related quality-of-life. These findings support the need for FMD and mental health screening and support in SCAD survivors.

Introduction

Ischaemic heart disease, including acute coronary syndrome (ACS) remains the leading cause of mortality over the world [1]. ACS also has significant impacts on the quality-of-life (QoL) of its survivors [2-4]. Spontaneous coronary artery dissection (SCAD) is an important and increasingly recognised cause of ACS. SCAD is characterised by the separation between any two of the three layers (intima, media, adventitia) of the coronary artery, forming an intramural haematoma, that happens spontaneously (i.e., not related to atherosclerotic, traumatic, or iatrogenic causes) [5-8]. The resulting intramural haematoma can obstruct coronary flow and may or may not communicate with the true lumen. SCAD particularly affects mostly younger, female patients, without traditional risk factors for cardiovascular disease [5-8]. Consensus documents on the management of SCAD have been published by international professional societies [6-8]. Although the overall percentage of SCAD is only about 1-4% in all cases of ACS, it accounts for up to 30% of ACS in women under the age of 50 [9-13]. In pregnant women, SCAD is among the most common causes of myocardial infarction [14]. In one study, SCAD was the most common cause of pregnancy-related myocardial infarction at 43% [14]. In many cases, SCAD can be triggered by physical activity and emotional stress [15, 16]. Compared to women, men with SCAD are younger and more likely to have physical than emotional stress reported as a trigger of SCAD [17]. SCAD usually affects people at a young age, where full-time work and caring for young children are prevalent. This means that any event has the potential for profound impact on well-being and quality-of-life. Previous qualitative studies have reported a significant impact of SCAD on the lifestyle and psychosocial well-being of survivors [18, 19]. However, these past studies have been limited by small numbers and potential for selection bias. Data on the aspects of

health-related quality-of-life is important in our understanding of the consequences of SCAD on survivors' lives. This may also serve as a basis to improve their well-being in the future. This study aimed to assess the 30-day health-related quality-of-life (HRQoL) and its determinants in a large prospective cohort of survivors of SCAD-related ACS.

Materials and method

Study design

The Australian-New Zealand SCAD Registry is a multi-centre cohort study across 23 hospitals in Australia and New Zealand. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12621000824864). Ethics approval was obtained from 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. The registry comprised a retrospective arm and a prospective arm, with this current study including only participants in the prospective arm who all gave their informed consent. The protocol for this registry has been published previously [20].

People aged 18 years and older who were hospitalised with an ACS caused by SCAD gave their informed consent to participate in the registry. Anonymised invasive coronary angiography images for all patients (as well as intravascular imaging and computed tomography coronary angiography, where performed) were uploaded to a secure online image database hosted by the University of Sydney. Core laboratory adjudication was performed, and only patients deemed to have SCAD after adjudication were included in the registry.

Study data was collected and managed using REDCap, a secure, web-based data software platform hosted by the University of Sydney. For all prospective participants, baseline clinical information was obtained from their hospital medical records alongside participant-completed questionnaires performed at the time of recruitment, 30 days, and then yearly thereafter for up to five years. Follow up questionnaires were administered via email link to the online questionnaire with telephone calls for those who did not respond or who required the use of an interpreter.

Participants completed the HRQoL assessment using the EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) instrument at the 30-day follow-up [21]. The EQ-5D has previously been used to study HRQoL of people with SCAD as well as other cardiovascular diseases [22-24]. This instrument consists of five domains: mobility, personal care, usual activities, pain or discomfort, and anxiety or depression. For each domain, the participant selected one of the three levels: level one means no difficulty with the domain, level two means moderate difficulty with the domain, and level three means severe or extreme difficulty with the domain. From these domains, a summary index score was calculated for all patients using a formula validated for the Australian population [25]. For the EQ-5D visual analogue scale (VAS), patients were asked to rate their health on a scale from 0 to 100, with 0 meaning the worst health they could imagine and 100 meaning the best health they could imagine.

The primary endpoint was health-related quality-of-life at 30 days after the index SCAD-related ACS event, as measured by the EQ-5D summary index score and the VAS score. Secondary endpoints included each component of the EQ-5D questionnaire.

Statistical analysis

Participants who fully completed the EQ-5D questionnaire at 30 days were included in the analysis. Means and standard deviations were calculated for normally distributed variables while medians and inter-quartile ranges were used for those with non-normal distribution. Counts and proportions were used for categorical variables. A two-tailed p value of <0.05 was considered statistically significant. Univariable and multi-variable beta regression models were used to assess determinants of HRQoL. Univariable and multi-variable logistic regression models were used to assess determinants of each domain of the EQ-5D questionnaire. Variables used in the both the beta regression multivariable model and logistic regression multivariable model were based on clinical reasoning and previous literature, and included age, sex, type of ACS (ST elevation vs non-ST-elevation ACS), left ventricular systolic dysfunction (LVSD, defined as left ventricular ejection fraction ≤40%), proximal coronary artery involvement, multivessel SCAD, and the presence of fibromuscular dysplasia (FMD). FMD is a vascular disorder characterised by abnormal cellular proliferation and distorted histological structure of the arterial wall, typically manifesting as a string of beads appearance on imaging [26]. Past studies have demonstrated a significant association between FMD and SCAD, with the prevalence of FMD ranging from 30% to nearly 80% in people with SCAD who receive screening [15, 22, 27-32]. Statistical analysis was performed using the RStudio software with the use of the tidyverse, skimr, eq5d and betareg packages [26-29].

Results

From September 2021 to January 2025, 233 patients with SCAD were prospectively recruited of whom 193 (82.8%) fully completed the 30-day EQ-5D questionnaire and were included for analysis. Baseline characteristics of the cohort are summarised in

Table 1, with a mean age of 52.7±10.7 years, 89.1% females, mean body mass index (BMI) of 28.2±6.2 kg/m^2 and 82.4% Caucasian. At least one standard cardiovascular risk factor was present in 50.8%, with hypertension the most common at 30.1%, followed by dyslipidaemia (22.3%), a family history of premature coronary artery disease (19.2%) and diabetes mellitus (2.1%). At total of 33.7% of participants presented with ST elevation myocardial infarction (STEMI). A trigger event for SCAD was self-reported in 156 people (80.8%), with emotional stress the most common trigger (149/193, 77.2%) and physical stress the second most common trigger 42/193 (21.8%). Percutaneous coronary intervention (PCI) was performed in 11.4%, and 8.8% had impaired left ventricular ejection fraction ≤40%. Comparison between those who completed and those who did not complete the EQ-5D questionnaire was given in supplementary table 2. Responders were more likely to be female (89.1% vs 69.7%, p=0.002) and to be Caucasian (82.4% vs 62.5%, p=0.005).

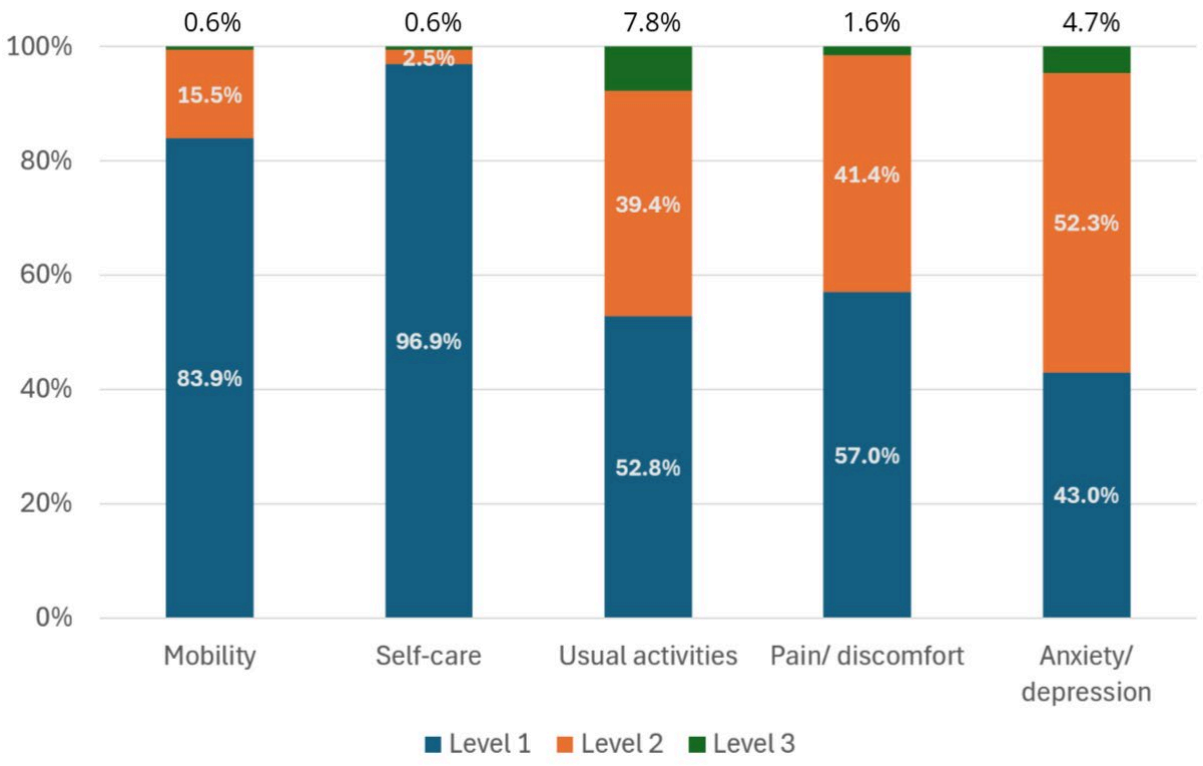
Table 1 – Baseline characteristics of SCAD survivors who completed the 30-day Quality-of-life assessment (n=193)

Characteristics	Number (%)
Age at SCAD diagnosis, mean±SD (years)	52.7±10.7
Female sex	172 (89.1%)
Body Mass Index, mean±SD (kg/m^2)	28.2±6.2
Ethnicity	
• Caucasian	159 (82.4%)
• East Asian	8 (4.1%)
• South Asian	4 (2.1%)
• Aboriginal & Torres Strait Islander	2 (1.0%)
• African	2 (1.0%)
• Maori	7 (3.6%)
• Pacific People	1 (0.5%)
• Middle Eastern and Northern Africa	8 (4.1%)
• Other/ Unknown	9 (4.6%)
Background medical history	
• Family history of premature CAD	37 (19.2%)
• Hypertension	58 (30.1%)
• Diabetes	4 (2.1%)
• Dyslipidaemia	43 (22.3%)
• Stroke/TIA	1 (0.5%)
• Fibromuscular dysplasia	3 (1.6%)
• Depression	36 (18.7%)
• Anxiety	33 (17.1%)

Number of pregnancies of female participants 0 1-3 ≥4 Missing/ unknown	 20 111 35 6
Current or ex-smoker	59 (30.7%)
Pregnancy associated SCAD (Females, n=172)	25 (14.5%)
Physical stress as SCAD trigger Emotional stress as SCAD trigger	42 (21.8%) 149 (77.2%)
Type of ACS • ST elevation myocardial infarction • Non-ST elevation ACS	 65 (33.7%) 128 (66.3%)
Percutaneous coronary intervention performed	22 (11.4%)
LVEF assessed - Of those assessed, LVEF≤40%	171 (88.6%) 15 (8.8%)
Screening performed for FMD: Among those screened, FMD detected Vascular abnormalities not meeting FMD criteria	132 (68.4%) 39 (29.5%) 15 (11.4%)

ACS: acute coronary syndrome, CAD: coronary artery disease, SCAD: spontaneous coronary artery dissection, SD: standard deviation, FMD: fibromuscular dysplasia, LVEF: left ventricular ejection fraction, TIA: transient ischaemic attack

Figure 1 - Summary of components of the EQ-5D questionnaire (n=193)



At a median of 33 (interquartile range 30-89) days from the index SCAD event, the mean EQ-5D index summary score was 0.77±0.19 and mean EQ-5D VAS score was 68.5±17.1. Each component of the EQ-5D questionnaire is summarised in Figure 1. A total of 16.1% of patients reported problems with walking, 3.1% problems with personal care, 47.2% had problems with performing usual activities, 43.0% reported at least moderate pain or discomfort and 57.0% reported at least moderate anxiety or depression. Further breakdown of EQ-5D health profiles is shown in supplementary table 1.

Age, sex, type of ACS, the presence of left ventricular systolic dysfunction, proximal vessel involvement, and multivessel involvement were not associated with the EQ-5D summary index score on both the univariable and multivariable beta regression models. FMD was associated with worse EQ-5D summary index score in both the

univariable (mean EQ-5D summary index score 0.71 vs 0.79, p=0.004) and multi-variable models (p=0.005). For the EQ-5D VAS score, female sex was an independent predictor of a lower score on multivariable analysis (mean VAS score 74.9 vs 67.7, p=0.086 in the univariable and p=0.039 in the multi-variable model). FMD (mean VAS score 17.2 vs 16.0, p=0.066 in the multi-variable model) and younger age (p=0.541 in the multivariable model) were associated with lower VAS scores, but did not meet statistical significance. Beta-regression analyses results of the EQ-5D summary index score and VAS score are reported in Table 2 and Table 3, respectively.

Table 2 - Association between EQ-5D summary index score and key variables

Variables	**Mean EQ-5D index score (standard deviation)**	**p value of univariable model**	**p value of multivariable model**
Age		0.62	0.47
<50	0.76 (0.21)		
≥50	0.77 (0.17)		
Sex		0.67	0.55
Male	0.80 (0.19)		
Female	0.77 (0.19)		
Type of ACS		0.15	0.21
STEMI	0.80 (0.15)		
NSTE-ACS	0.76 (0.20)		
Left ventricular systolic dysfunction		0.74	0.97
LVEF<40%	0.76 (0.20)		
LVEF≥40%	0.77 (0.10)		

Proximal vessel involved Non-proximal vessel involved	0.78 (0.18) 0.77 (0.18)	0.98	0.81
Multiple vessels involved Single vessels involved	0.77 (0.13) 0.77 (0.19)	0.73	0.66
FMD present FMD not present	0.71 (0.17) 0.79 (0.19)	0.004 *	0.005 *

ACS: acute coronary syndrome; FMD: fibromuscular dysplasia; LVEF: left ventricular ejection fraction; NSTE: non-ST-elevation; STEMI: ST-elevation myocardial infarction

* indicates variables with p value <0.05

Age, sex, type of ACS (ST elevation vs non-ST-elevation ACS), left ventricular systolic dysfunction (defined as left ventricular ejection fraction ≤40%), proximal coronary artery involvement, multi-vessel SCAD, and the presence of fibromuscular dysplasia (FMD) were all in the multivariable model

Table 3 - Association between EQ-5D visual analogue scale and other variables

Variables	Mean EQ-5D VAS score (standard deviation)	p value of univariable model	p value of multivariable model†
Age		0.10	0.054 †
<50	65.8 (17.9)		
≥50	70.0 (16.5)		
Sex		0.09	0.039 *
Male	74.9 (15.2)		
Female	67.7 (17.2)		
Type of ACS		0.68	0.49
STEMI	69.5 (18.1)		
NSTE-ACS	68.0 (15.0)		
Left ventricular systolic dysfunction		0.30	0.18
LVEF≤40%	63.7 (19.4)		
LVEF>40%	68.4 (17.1)		
Proximal vessel involved	67.6 (17.5)	0.85	0.95
Non-proximal vessel involved	68.6 (17.2)		
Multiple vessels involved	70.6 (18.9)	0.52	0.31
Single vessels involved	68.3 (17.0)		
FMD present	64.3 (17.2)	0.058 †	0.066 †
FMD not present	69.6 (16.0)		

ACS: acute coronary syndrome; FMD: fibromuscular dysplasia; LVEF: left ventricular ejection fraction; NSTE: non-ST-elevation; STEMI: ST-elevation myocardial infarction

* indicates variables with p value <0.05; † indicates variables with p value <0.10

Age, sex, type of ACS (ST elevation vs non-ST-elevation ACS), left ventricular systolic dysfunction (defined as left ventricular ejection fraction ≤40%), proximal coronary artery involvement, multi-vessel SCAD, and the presence of fibromuscular dysplasia (FMD) were all in the multivariable model

The results of logistic regression models are shown in Tables 4 and 5. FMD was an independent predictor of difficulties with usual activities (adjusted odds ratio [aOR] 2.87, 95% confidence interval [CI] 1.31-6.63, p=0.011) and anxiety/ depression (aOR 2.60, 95%CI 1.14-6.41, p=0.029). FMD was also associated with a trend for higher levels of pain or discomfort, which did not meet statistical significance (aOR 2.04, 95%CI 0.95-4.46, p=0.068).

Table 4 - Univariable logistic regression model of each components of the EQ-5D questionnaire

Variables	Mobility	Personal care	Usual activities	Pain/ Discomfort	Anxiety/ Depression
Age	1.01 (0.97-1.05)	0.96 (0.88-1.04)	1.00 (0.98-1.03)	0.99 (0.97-1.02)	0.99 (0.96-1.01)
Female sex	0.79 (0.27-2.91)	1.14 (NA)	1.52 (0.61-4.00)	1.58 (0.63-4.36)	1.90 (0.76-4.88)
STEMI	0.77 (0.32-1.73)	0.98 (0.13-5.14)	1.23 (0.67-2.24)	1.12 (0.61-2.06)	0.63 (0.34-1.15)
LVEF ≤40%	0.34 (0.02-1.81)	2.16 (0.19-14.7)	1.27 (0.43-3.77)	0.86 (0.28-2.51)	1.55 (0.52-5.16)
Proximal vessel involvement	1.21 (0.33-3.57)	1.55 (0.08-10.25)	0.74 (0.29-1.81)	1.40 (0.57-3.45)	0.60 (0.24-1.46)
Multiple vessels involvement	0.50 (0.08-1.96)	1.56 (0.08-10.32)	1.17 (0.47-2.87)	1.38 (0.56-3.40)	0.60 (0.24-1.48)
FMD	1.80 (0.72-4.21)	2.03 (0.27-10.80)	2.74 * (1.33-5.88)	1.73 (0.85-3.54)	2.24 * (1.06-4.98)

FMD: fibromuscular dysplasia, LVEF: left ventricular systolic dysfunction, STEMI: ST-elevation myocardial infarction,

Numbers are odds ratio (95% confidence interval); * indicates variable with p value <0.05

Table 5 - Multi-variable logistic regression model of each component of the EQ-5D questionnaire

Variables	Mobility	Personal care	Usual activities	Pain/ Discomfort	Anxiety/ Depression
Age	1.01 (0.97-1.05)	0.95 (0.87-1.03)	1.00 (0.97-1.03)	1.00 (0.97-1.03)	0.98 (0.95-1.01)
Female sex	0.85 (0.27-3.22)	NA	1.53 (0.58-4.25)	1.53 (0.58-4.34)	2.25 (0.86-6.14)
STEMI	0.85 (0.32-2.05)	0.67 (0.08-3.96)	1.45 (0.74-2.86)	1.12 (0.57-2.18)	0.60 (0.30-1.18)
LVEF ≤40%	0.41 (0.02-2.33)	2.03 (0.08-18.9)	1.18 (0.37-3.74)	0.78 (0.23-2.41)	2.18 (0.68-8.03)
Proximal vessel involvement	0.94 (0.20-3.17)	1.19 (0.05-9.10)	0.51 (0.17-1.36)	1.10 (0.41-2.86)	0.55 (0.20-1.48)
Multiple vessel involvement	0.61 (0.09-2.37)	1.34 (0.06-10.6)	0.96 (0.35-2.58)	1.39 (0.52-3.73)	0.48 (0.17-1.30)
FMD	1.57 (0.58-3.94)	2.18 (0.28-12.6)	2.70 * (1.25-6.11)	2.04 † (0.95-4.46)	2.60 * (1.14-6.41)

FMD: fibromuscular dysplasia, LVEF: left ventricular systolic dysfunction, STEMI: ST-elevation myocardial infarction,

Numbers are odds ratio (95% confidence interval); * indicates variable with p value <0.05* indicates variable with p value <0.05, † indicates variables with p value <0.1.

Discussion

This multicentre cohort study explored the health-related quality-of-life in prospectively recruited patients with core laboratory-confirmed SCAD from 23 hospitals and 2 countries. At 30 days after the index event, SCAD survivors had low mean EQ-5D summary index scores of 0.77 and low mean EQ-5D VAS scores of 0.69. The main contributors to poor health-related quality-of-life in SCAD survivors included high rates of pain and discomfort, difficulties with usual activities, and anxiety or depression. After controlling for confounding factors, FMD was found to be independently associated with lower EQ-5D summary index scores, while female sex was independently associated with a lower EQ-5D VAS score.

In the current study, the average EQ-5D index score of 0.77 in people with a SCAD-related ACS was significantly lower than the Australian norm of 0.87 ($p<0.001$ on one-sample t-test) [30]. However, this comparison is limited by the population norm being 50% female and half over the age of 50, compared to the current cohort of SCAD survivors who were 89% female and an average age of 52 years. The health-related quality-of-life of SCAD survivors has not been extensively studied. One recent survey of 172 SCAD survivors in an Australian study reported a mean EQ-5D summary index score of 0.79 and mean EQ-5D VAS score of 0.72 at a median of 22 months from the first diagnosis of SCAD [22]. These results, which were limited by the survey response rate of 14.5%, are similar to the current study findings and support that health-related quality-of-life of SCAD survivors is poor after the index ACS event and, does not appear to improve after nearly two years.

Atherothrombotic ACS has been known to affect the health-related quality-of-life of survivors. In a large Australian study involving 10,812 patients (23.1% female), health-related quality-of-life was assessed at 30 days after ACS using the EQ-5D

questionnaire [4]. Compared to this cohort of patients with atherothrombotic ACS, SCAD survivors in our cohort had lower EQ-5D summary index scores (mean 0.77 vs median 1.0) and lower VAS scores (mean 68.5 vs median 80.0), despite being a younger population. In further comparison of the domains, the current study found that 47% and 43% of people with SCAD reported being affected in the domains of usual activities and pain/discomfort, compared to 19% and 14% of patients with atherothrombotic ACS, respectively. Anxiety and depression were also reported in a high proportion of patients with SCAD at 57%, compared to 19% of patients with atherothrombotic ACS from this past study. While these comparisons are limited by differences in demographics of these two cohorts, our findings demonstrate that SCAD-related ACS has significant impacts on health-related quality-of-life that are at least comparable to, if not higher than, that of ACS from atherosclerosis.

In the current study, FMD was shown to be a significant predictor of poorer health-related quality-of-life, with lower summary index scores. Importantly, previous studies have demonstrated an association between the presence of FMD and an increased risk of SCAD recurrence and major adverse cardiovascular events (MACE) [15, 38]. This higher risk of SCAD recurrence and MACE may explain the poorer health-related quality-of-life experienced by SCAD survivors. In the current study, SCAD survivors with FMD were 2.7 times more likely to experience difficulties with performing usual activities. It is possible that patients with FMD may have a higher risk of symptomatic heart failure as part of their higher risk of MACE, thus having more difficulty in performing their usual activities. In addition, survivors who had FMD were 2.6 times more likely to have at least moderate levels of anxiety or depression. Patients with a higher risk of MACE and SCAD recurrence may likely feel more anxious or depressed about their condition, resulting in a poorer mental health domain. The current study

adds to the importance of FMD in patients with SCAD and is the first to associate this with poorer health-related quality-of-life [39]. These findings emphasise the need to perform screening for FMD in all patients with SCAD in accordance with the consensus recommendations from professional cardiology societies [6, 8].

In the current study, the prevalence of mental health disorders was high and above that reported in the general population. The baseline depression and anxiety prevalence was 19% and 17% respectively, compared to a reported 12% and 8% in the general Australian population as reported by the Australian Bureau of Statistics [40]. After the development of SCAD, 57% of survivors reported at least moderate levels of anxiety or depression, early after the event (average of 33 days). This is consistent with prior studies demonstrating a significant impact of a SCAD event with reported high rates of depression, anxiety, and post-traumatic stress disorder [18, 22, 41]. Our study supports the current recommendations of professional societies on the active screening and management of mental health conditions in people presenting with SCAD [6-8].

Female sex has been found to be associated with worse HRQoL in patients with atherothrombotic ACS [4, 42]. The current study is the first to demonstrate a similar finding in people suffering from SCAD-induced ACS. After controlling for potential confounders, we found that females had poorer HRQoL as measured by the EQ-5D VAS score, with a mean score of 68 in females compared to 75 in males. In the current study, 59% of women reported at least moderate symptoms of anxiety or depression, compared to 43% in men. There could be multiple reasons for this discrepancy between the sexes. Firstly, the diagnosis of ACS and SCAD might be delayed in young women, leading to a delay in appropriate management. Previous studies have reported less serious treatment of women with SCAD in the emergency department,

and many patients were not diagnosed with SCAD at the time of myocardial infarction [22, 43]. Secondly, being female may be perceived as having a higher risk of SCAD recurrence. This is because SCAD is thought to be associated with both endogenous and exogenous female hormones, and FMD, associated with SCAD recurrence, is also a female-predominant condition. Compared to men, women may also have the added consideration of avoiding further pregnancy and exogenous sex hormones. SCAD has been found to be associated with pregnancy and when this occurs, appears to have worse clinical outcomes such as higher risk of ST-elevation myocardial infarction, involvement of the left main or multiple coronary arteries, left ventricular systolic dysfunction, cardiogenic shock, and invasive intervention [44-46]. Given that SCAD affects an 85-90% female predominant cohort, the finding of lower quality-of-life in women is concerning and should trigger future research in this area.

Limitations

The current study was limited by its observational nature and, despite being the largest study to date in Australia and New Zealand on the HRQoL of SCAD survivors, the sample size was still relatively low at just under 200. Most participating study sites were major tertiary hospitals, which may limit the ability to generalise study results to the general population of patients treated with SCAD. In addition, 17.2% prospectively recruited participants did not complete the EQ-5D and were excluded from the analysis. Participants who did not complete the EQ-5D survey were generally similar to those who did, except for a smaller proportion of females. The people who did not complete the questionnaire had lower female percentage and were less likely to be Caucasians but similar in other baseline parameters. The type (cardiac, musculoskeletal, …) of pain/ discomfort were not collected in this study, which may

limit its clinical interpretation. To avoid over-adjustment and obscuring associations of clinical relevance, pre-existing psychiatric conditions were not included in the multivariable model as mental health is a core domain within the EQ-5D, and the two are highly correlated.

Conclusions

SCAD is an important cause of ACS and has significant impacts on HRQoL. Compared to both the general population and an atherothrombotic ACS cohort, people with SCAD had low overall HRQoL and high rates of mental health issues comprising anxiety and depression. FMD was an independent predictor of poorer HRQoL and supports the need for FMD screening in people with SCAD. Quality of life in females with SCAD was worse than in males with SCAD, and future research should address the particular needs of female survivors, including support for mental health and strategies to reduce anxiety.

Data statement

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

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Author Contributions

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MZ: Investigation; Writing - review & editing

PP: Investigation; Writing - review & editing

JC: Investigation; Writing - review & editing

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DM: Investigation; Writing - review & editing

LK: Investigation; Writing - review & editing

NJ: Investigation; Writing - review & editing

SF: Investigation; Writing - review & editing

AI: Investigation; Writing - review & editing

JL: Investigation; Writing - review & editing

RZ: Investigation; Writing - review & editing

SEJ: Investigation; Writing - review & editing

NP: Investigation; Writing - review & editing

ED: Investigation; Writing - review & editing

IS: Investigation; Writing - review & editing

RA: Investigation; Writing - review & editing

MW: Investigation; Writing - review & editing

HZL: Investigation; Writing - review & editing

RB: Investigation; Writing - review & editing

EWL: Investigation; Writing - review & editing

RB: Investigation; Writing - review & editing

TF: Investigation; Writing - review & editing

SL: Investigation; Writing - review & editing

KM: Investigation; Writing - review & editing

SM: Data curation; Formal analysis; Methodology; Software; Validation; Visualization; Writing - review & editing

SZ: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing - review & editing

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Preamble to the next chapter

This chapter explores the short-term quality-of-life of SCAD survivors and its determinants. It demonstrates lower quality-of-life experienced by SCAD survivors shortly after the index event, and the correlation between lower quality-of-life with FMD and female sex. This is also the last original study of this thesis. The next chapter summarises findings of all the previous chapters, discusses their relationships and implications, provides a conclusion, and suggests future research direction.

CHAPTER 9: DISCUSSIONS AND CONCLUSIONS

Clinical presentation, treatment, and outcomes of spontaneous coronary artery dissection (SCAD)

This thesis has illustrated, in the largest Australian New Zealand SCAD cohort to date, the predilection of SCAD to occur in middle-aged women, who have a low prevalence of traditional cardiovascular risk factors. On long-term follow-up, the rate of major adverse cardiovascular events (MACE) was high at 8.6%, comparable to outcomes following atherosclerotic acute coronary syndrome (ACS) [1-4]. Importantly, this thesis found new and clinically relevant associations with adverse outcomes in SCAD survivors. Namely, that oral anticoagulation use, dual-antiplatelet therapy comprising aspirin and ticagrelor, a history of stroke, and the presence of fibromuscular dysplasia (FMD) were all associated with increased MACE. The latter three factors were also associated with increased risk of recurrence. In contrast to previous research, beta-blocker use was not found to be associated with a reduction in SCAD recurrence [5] however, a high proportion of patients were taking beta blockers at discharge.

These findings are clinically relevant, as they support the hypothesis that the primary pathogenesis of SCAD is a bleed, rather than a tear, due to vasa vasorum rupture as the initiating event [6, 7]. Our findings are further supported by a recent study showing increased risk of MACE in patients receiving dual-antiplatelet therapy (DAPT) compared to those on single-antiplatelet therapy (SAPT) [8]. This thesis added to this finding by demonstrating that the increased risk of MACE and recurrence was associated with the dual-antiplatelet regimen comprising ticagrelor, but not with the regimen comprising clopidogrel (where ticagrelor is a more potent antiplatelet agent). These results add significantly to our knowledge of SCAD being predominantly caused

by the outside-in mechanism, with intramural haematoma formation as the initiating event. Further, the results of this thesis call for caution in the use of oral anticoagulation and more potent antiplatelet therapy in patients with SCAD. Because most patients with SCAD were treated with DAPT (64% in our Australian New Zealand cohort) and the use of DAPT comprising ticagrelor was common (over 50% of those who were on DAPT), the findings from this thesis are likely to have a significant, practice-changing impact; without any randomised controlled trial data to guide management, the treatment of SCAD is reliant on observational findings and, likely, practice of using DAPT with more potent antiplatelet therapy in SCAD will decline.

Quality-of-care of patients with SCAD and its determinants

Significant gaps in the care of patients with SCAD have been identified in previous literature. Up to one-third of patients with SCAD were not correctly diagnosed at the time of first medical contact, and patients reported a perceived lack of knowledge of their treating clinicians about SCAD [9-11]. Many patients found the internet to be a more helpful source of information than their health care professionals. This thesis assessed the quality-of-care of patients with SCAD both through the level of adherence to consensus recommendations and through patients' self-reported experience.

In the first analysis, this thesis demonstrated that adherence to the recommended use of pharmacotherapies, including the use of at least a single antiplatelet agent as well as a beta-blocker, was high, at more than 80%, while cardiac rehabilitation referral was slightly lower, at just over 70%. The rate of FMD screening in patients with SCAD appeared low and varied significantly across the world. In our Australian New Zealand

cohort, less than half of patients with SCAD were screened for FMD, despite this being a recommendation for all patients. While FMD screening did significantly improve over time, which was an encouraging signal, it remained much lower than expected. This highlights an important finding for clinician education on the role of FMD screening; even more important given our findings from Chapter 4, that the presence of FMD is significantly associated with adverse MACE outcomes.

Chapter 7 showed that only 66% of patients felt that their symptoms were treated seriously as a heart attack in the emergency department, and just over half of the patients were satisfied with the information about SCAD provided by their doctors. Less than 20% of patients reported receiving the most useful information about SCAD from their healthcare providers; instead, nearly 80% reported the internet and support groups as their most useful sources of information. These results demonstrated the gap in medical professionals' knowledge of SCAD (as perceived by patients) and may reflect a broader lack of awareness about SCAD among clinicians. Despite this finding, patients still rated their quality-of-care as high (median score of 8 out of 10). This may reflect contemporary pathways in the stratification of chest pain presentation whereby the use of early high sensitivity troponins and chest pain pathways means that patients who would otherwise be perceived to be at low risk of ACS (young, female, no traditional cardiovascular risk factors) have early detection of an ACS – and receive appropriate care, despite clinicians perhaps being unaware of the SCAD diagnosis.

Quality-of-life of SCAD survivors and its determinants

Chapters 7 and 8 made important contributions to our understanding of the quality-of-life of SCAD survivors, which has not been well studied before. The thesis objectively

assessed the quality-of-life using the EQ-5D-3L questionnaire, a well-validated tool to assess quality-of-life in cardiovascular medicine [12, 13]. This tool has been used in two different cohorts, comprising a total of 365 patients. SCAD appeared to have a significant impact on the quality-of-life of survivors, with the EQ-5D summary index score at 30 days significantly lower than the population mean and comparable to people with atherosclerotic ACS. The EQ-5D summary index score and EQ-5D visual analogue score (VAS) in chapter 7's cohort of patients with a median follow-up of 22 months after the index SCAD event remained low. FMD was an independent predictor of a lower EQ-5D summary index score. Younger women also had worse quality-of-life compared to men, with female sex and younger age being independently associated with lower EQ-5D VAS scores. Quality-of-life was mainly affected by difficulties with performing usual activities, pain or discomfort, and anxiety or depression. These findings have important clinical implications – people with SCAD have high rates of pain, discomfort, and anxiety and depression. This should be the focus of both further work as well as research that focuses on implementation of strategies to mitigate this, such as early mental health assessments for SCAD survivors, female or SCAD-specific cardiac rehabilitation, and timely investigation for, and management of, pain.

The role of FMD in SCAD

FMD was known to be the most common vascular abnormality associated with SCAD [6, 7]. Throughout this thesis, FMD has emerged as an important factor linked to the pathogenesis of SCAD as well as an independent prognosticator in SCAD survivors. The association between SCAD and FMD, as demonstrated in our Australia-New Zealand cohort, is clear – in patients screened, FMD is found in a third of SCAD

survivors. In addition, this thesis demonstrated the association of FMD with a more than 2-fold increased risk of MACE, with the added insight that this was driven mainly by the increased risk of SCAD recurrence [14]. The association between FMD and SCAD was thought to be due to a weakened arterial wall, which predisposes to SCAD through the formation and propagation of an intramural haematoma. This predisposition could also explain why patients with FMD had a higher risk of recurrence and MACE. Chapter 8 was the first study to demonstrate further that patients with SCAD and FMD experienced worse short-term quality-of-life after SCAD. It is possible that, due to the reduced vascular wall integrity, SCAD lesions in patients with FMD might take longer to heal or might not heal completely. Therefore, patients with FMD may experience more chest pain or discomfort, which results in a worse quality-of-life. Further research is needed to explore this hypothesis. Despite the importance of FMD in patients with SCAD highlighted throughout this thesis, Chapter 4 found that FMD screening was the least adhered to quality-of-care parameter, representing a significant care gap. As the ANZ-SCAD Registry involved mostly large tertiary hospitals, the real-life practice of FMD screening was likely to be even lower. The findings from this thesis can be used to raise awareness among clinicians and advocate for FMD screening of all patients with SCAD in the future.

Strengths and limitations

Most of the original studies in this thesis utilised data from the ANZ-SCAD Registry, one of the largest cohort studies on SCAD worldwide. In addition to the large sample size, this Registry also had the important feature of core laboratory adjudication of diagnostic imaging. As the diagnosis of SCAD can be challenging, core laboratory adjudication ensures that only patients with an accurate diagnosis of SCAD were

included in the Registry, thus maintaining the high quality of the data and minimising bias. Five chapters from this thesis have been published in peer-reviewed journals, including the prestigious European Heart Journal, which has an impact factor of 39.3. In addition, many of the original studies in this thesis were presented at international conferences, including the European Society of Cardiology Congress, the world's largest cardiology conference. These presentations helped increase the exposure of the studies and potentially enhanced their real-world impact. The main limitation of this thesis was that all the data were from non-randomised studies. Although efforts have been made to control for confounding factors, the potential for bias could not be eliminated.

Future research directions

This thesis provides the groundwork to guide future research with specific questions to be addressed:

1. Antiplatelet therapy has been used routinely in people with ACS due to the predominant mechanism being atherosclerotic plaque rupture and thrombus formation. The observational findings in the current thesis that more potent antiplatelet therapy may be harmful in patients with SCAD require confirmation in large, randomised controlled trials, powered to look for MACE outcomes. The type and optimal duration of antiplatelet therapy also need to be determined.
2. Beta-blockers were not found to be associated with a lower risk of MACE or SCAD recurrence in the current thesis, despite this being standard of care. Future work with data pooling to obtain large, diverse cohorts of patients with

SCAD is needed to determine if beta-blockers are beneficial in contemporary care of SCAD patients.

3. This thesis found that the rates of FMD in people with SCAD were high at approximately 30% however, this was limited by very low rates of FMD screening in our Australian/New Zealand population. The true prevalence of FMD among patients with SCAD requires further studies with rigorous use of FMD screening in all SCAD survivors.
4. While cardiac rehabilitation referral was reasonable, it was still less than ideal, and attendance was lower; identification of the barriers to cardiac rehabilitation attendance in these predominantly younger, female patients and ways to improve this requires further study.
5. A sex gap was identified between women and men in self-reported quality-of-life following a SCAD event; ways to address this gap are needed.

Conclusion

This thesis has advanced our understanding of the pathogenesis and management of SCAD by identifying treatment- and patient-related factors associated with adverse outcomes, including more potent dual antiplatelet therapy, oral anticoagulation and FMD. It highlights the profound and enduring impact of SCAD on survivors' quality-of-life and uncovers disparities in care by age and sex. These findings emphasise the importance of FMD screening, consistent application of consensus-recommended care, and tailored support for patients. Looking ahead, the findings from this thesis provide a foundation for study into management strategies, informing future clinical trials, and ideally improving long-term outcomes and well-being for people with SCAD.

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APPENDIX

Chapter 4: Supplementary materials for paper 1

Project ID	2021/PID00042
Ethics Ref:	2021/ETH00040
Governance Ref:	2021/STE00059; 2021/STE00060; 2021/STE00061; 2021/STE00062; 2021/STE00063; 2021/STE00064; 2021/STE00065

24 February 2021

A/Prof Sarah Zaman
Department of Academic Interventional Cardiology
Westmead Hospital, Westmead Applied Research Centre (WARC)

Dear A/Prof Zaman

Project title: The Australian New Zealand Spontaneous Coronary Artery Dissection (ANZ-SCAD) Registry

Thank you for your correspondence addressing the matters raised in the HREC's letter dated 9 February 2021 following single ethical review of the above project at its meeting held on 2 February 2021.

This HREC has been accredited by the NSW Department of Health as a lead HREC to provide the single ethical and scientific review of proposals to conduct research within the NSW public health system. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research and the CPMP/ICH Note for Guidance on Good Clinical Practice.
This proposal meets the requirements of the National Statement and I am pleased to advise that the HREC has now granted ethical approval of this research project to be conducted at:

- Westmead Hospital - Principal Investigator A/Prof Sarah Zaman
- Blacktown Hospital - Principal Investigator Dr David Burgess
- Nepean Hospital - Principal Investigator Sonya Burgess
- Liverpool Hospital - Principal Investigator Dr Sidney Lo
- St George Hospital - Principal Investigator Dr Jennifer Yu
- John Hunter Hospital - Principal Investigator A/Prof Rohan Bhagwandeen
- Gosford Hospital - Principal Investigator Dr Tom Ford
- Monash Heart, Monash Health - Principal Investigator Dr Tony White
- Cabrini Hospital - Principal Investigator Dr Swati Mukherjee
- Box Hill Hospital - Principal Investigator A/Prof Jaya Chandrasekhar
- Alfred Hospital - Principal Investigator Prof Stephen Duffy
- Peninsula Health - Principal Investigator Prof Jaime Layland
- Fiona Stanley Hospital - Principal Investigator A/Prof Michael Nyugen
- Royal Adelaide Hospital - Principal Investigator A/Prof Peter Psaltis

The following documentation has been reviewed and approved by the HREC:

- HREA 2021/ETH00040, version 2, dated 9 February 2021
- Protocol, version 1 dated 13 January 2021
- Master - Participant Information Sheet and Consent Form, version 2, dated 9 February 2021
- Baseline CRF, version 1 dated 13 January 2021
- Baseline Patient Questionnaire CRF, version 1 dated 13 January 2021
- Follow up Questionnaire CRF, version 1 dated 13 January 2021
- Effective_Australia (English) EQ-5D-3L Paper Self-Complete, version 1 dated 13 January 2021
- ANZ-SCAD Clinical_endpoint questionnaires, version 1 dated 29 January 2021

Please note the following conditions of approval:

- The Coordinating Chief Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.
- For clinical trials of implantable medical devices only – The Coordinating Chief Investigator will confirm to the HREC that a process has been established for tracking the participant, with consent, for the lifetime of the device and will immediately report any device incidents to the Therapeutic Goods Administration (TGA).
- The Coordinating Chief Investigator will immediately report any protocol deviation / violation, together with details of the procedure put in place to ensure the deviation / violation does not recur.
- The Coordinating Chief Investigator will provide to the HREC in the specific format via REGIS, proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project. .
- The Coordinating Chief Investigator must notify the HREC, giving reasons, if the project is discontinued at a site before the expected date of completion.
- The Coordinating Chief Investigator must provide an annual report to the HREC and a final report at completion of the study, in the specified format.
- HREC approval is valid for 5 years contingent upon submission of an annual report via REGIS.
- The HREC has the discretion to adopt other appropriate mechanisms for monitoring depending on the complexity, design and risk perceived including
    1. Discussion of relevant aspects of the project with investigators, at any time,
    2. Random inspection of research sites, data or consent documentation,
    3. Interview with research participants or other forms of feedback from them, and
    4. Request and review reports from independent agencies such as a Data Safety Monitoring Board.
- If your research project is an interventional trial, please ensure it is registered on one of the clinical trial registries, eg http://www.actr.org.au.
- It should be noted that compliance with the ethical guidelines is entirely the responsibility of the Coordinating Chief Investigator.

You are reminded that this letter constitutes *ethical approval only*. You must not commence this research project until separate authorisation from the Chief Executive or delegate has been obtained.

In all future correspondence concerning this study, please quote Research Office File number ***(2021/PID00042).*** The HREC wishes you every success in your research.

Yours sincerely

Mrs Patricia Fa
Secretary
WSLHD Human Research Ethics Committee

cc: WSLHD Research Governance Manager

Participant Information Sheet/Consent Form

Non-Interventional Study

St. George Hospital

Title	Australia New Zealand Spontaneous Coronary Artery Dissection Registry
Short Title	*ANZ-SCAD Registry*
Project Sponsor	*The University of Sydney, Australia*
Coordinating Principal Investigator/ Principal Investigator	*Associate Professor. Sarah Zaman*
Associate Investigator(s)	*Dr. Richard Szirt*
Location	St. George Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, Australia New Zealand Spontaneous Coronary Artery Dissection (ANZ-SCAD) Registry. This is because you have been found to have had a spontaneous coronary artery dissection (SCAD) – often referred to as SCAD – that is an uncommon condition that occurs when a tear forms in a blood vessel in the heart. SCAD can slow or block blood flow to the heart, causing a heart attack, abnormalities in the heart rhythm, and sudden death. It is an emergency condition that is usually treated in hospital and diagnosed at the time of a coronary angiogram. SCAD most commonly affects women in their 40's or 50's, but it can occur at any age, and affect men. People who have SCAD often don't have typical risk factors for heart disease like high blood pressure, cholesterol or diabetes – yet are still often diagnosed with a heart attack. Unfortunately, SCAD has only recently been recognised as a major cause of heart attacks, particularly in young patients, and we don't fully understand what causes it, and the best way to treat it.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the research involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to the research that are described
• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The purpose of this study is to study patients who have had a diagnosis of SCAD.

As this condition is poorly understood, we want to study all aspects of SCAD, which include:

- What symptoms and signs are present when it is diagnosed?
- What is found on heart investigations in SCAD such as coronary angiography?
- What pre-existing conditions are associated with this disease?
- What treatment is being used in those who suffer from SCAD and are there some treatments that can prevent SCAD from occurring again?
- What proportions of patients with SCAD have another episode?

This will help us to find the best way to diagnose and treat SCAD as well as find what predicts recurrences. This study is completely observational and does not involve any extra tests or any changes to your treatment. However, the purpose is to collect information about SCAD in order to find better ways to diagnose and treat it, that could then be tested in further studies.

This research has been initiated by the study doctor, A/Professor Sarah Zaman from the University of Sydney and St. George Hospital. This research has been funded by a NSW Health government grant.

3 What does participation in this research involve?

If you agree to participate in the study, you will be asked to sign the Participant Information Sheet and Consent Form.

Your study participation will last for up to a maximum of 5 year(s) from the time of agreeing to participate, but you can stop participating at any stage.

Your participation will not involve any additional tests or treatment to what you have already receive/d through your treating hospital and doctors. As part of the study, your health information will be collected and recorded in a confidential, secure and de-identified manner in an online University database.

Following your admission to hospital with the diagnosis of SCAD, you will be contacted by a study nurse/co-ordinator to check if you would like to participate in this study. Information such as medical history, medications, blood tests and other underlying risk factors will be obtained from your medical records. After discharge you will also be contacted via email or telephone in order to complete a brief survey which will ask about any further hospital admissions, heart attacks or other new diagnoses, and current medication use. This contact will occur at 30 days, 12 months and then yearly thereafter for up to a maximum of 5 years, for as long as you agree to participate in the

study. We would also seek additional consent to see if you would be happy to be contacted in the future about other studies on SCAD that you may be eligible to participate in.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no costs associated with participating in this research project. You will not receive payments for participating in this study. You will not be charged for any part of this study.

It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we recommend that you inform them of your participation in this research project.

4 What do I have to do?

If you agree to join this research project, you will need to sign the consent form and then respond to the emailed survey's or answer the telephone at the above follow up times.

You will be asked for information such as about any further hospital admissions, chest pain symptoms, repeat heart scans, repeat heart attacks or other new diagnoses, and current medication use.

5 Other relevant information about the research project

This research project is a collaborative study conducted across multiple hospitals. About 850 people with SCAD will join in this research study across 16 hospitals in Australia and New Zealand. It is expected that 80 participants will be enrolled into the research project here at St. George Hospital.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with St. George Hospital.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. As this is an observational study, you will only be providing access to your data and responding to emails or telephone calls at the above specified follow-up times.

8 What are the possible benefits of taking part?

You may not derive a direct benefit from participation in the study. However, as part of this research, you will be helping us treat other patients with SCAD in the future.

9 What are the possible risks and disadvantages of taking part?

As this study is an observational study, all of the information that is collected for this research project is already documented in your standard medical history and there are no extra tests involved therefore no risks associated with this. We are only collecting data on what happens over time, there is no specific risk to taking part in this study.

The main disadvantage for yourself in participating is the small amount of time (~ 5-10 minutes each time) taken to complete an online or telephone survey at the follow up time points.

10 What if I withdraw from this research project?

If you decide to withdraw from this research project, please notify a member of the research team before you withdraw. This will not affect your ongoing treatment. Following your withdrawal, no further data will be collected. Information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. As your data will be de-identified at the time of collection and entering into the database (i.e. does not contain any personal identifying factors) you should be aware that data collected up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell the research team before you join the research project.

11 Could this research project be stopped unexpectedly?

It is unlikely that this research project would be stopped unexpectedly as it is observational in nature only. The only reason for stopping the research project prematurely would be due to cessation of funding however, we do not anticipate this to occur.

12 What happens when the research project ends?

After the study is completed, a summary of the results may be published at conferences or in medical journals. If the results of the study are presented to the public, you will not be named. Any data shared will not be identifiable.

Part 2 How is the research project being conducted?

13 What will happen to information about me?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal/health information about you for the research project. Any information obtained in connection with this research project that can identify you (such as name and/or address) will remain at your hospital and kept completely confidential. Any identifiable information will not be shared with anyone outside of your hospital without your permission. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law. All of the collected data that is entered into the secure database will be coded using a unique study number. Identifying data such as your name or address is not stored in the database. However, in order to perform the survey and follow-up's, your email and/or phone number will be entered into the database in order for automated generation of survey's to be sent to you at the pre-specified follow-up times. Your email and/or phone number will only be visible to the site and centralised study co-ordinator at the Westmead Applied Research Centre (WARC) from the University of Sydney and will be login and passport-protected. Telephone contact will only be performed if further clarification is required or surveys are not completed.

Any of your collected information at your treating hospital will be kept within the research department on a password-protected computer and within a locked filing cabinet. As above, only

your de-identified data will be used for research purposes. All data for this research project will be stored in an restricted access research facility for 7 years after the end of the study. After the 7 year period any data or information related to this study within the local hospital research department will be permanently deleted from the computer system and any hard copies will be destroyed.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained relevant to the study during the research project are subject to inspection for the purpose of verifying the procedures and the data. This review may be done by the relevant authorities and authorised representatives of the Sponsor, *The University of Sydney*, the institution relevant to this Participant Information Sheet, St. George Hospital, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant research personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information that is published or presented will not identify you.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or NSW privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

14 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

15 Who is organising and funding the research?

This research project is being conducted by study doctors at the University of Sydney and St George Hospital.

It is not a sponsored study, and there is no industry support. Research grants delivered by the University of Sydney are being used to fund this research. No member of the research team will receive a personal financial benefit from your involvement in this research project.

16 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of The Western Sydney Local Heath District and St. George Hospital.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

17 Further information and who to contact

The person you may need to contact will depend on the nature of your query.
If you want any further information concerning this project you can contact the principal study coordinator.

Clinical contact person

Name	*Dr. Richard Szirt*
Position	*Cardiologist*
Telephone	02 9113 1086
Email	*Richard.Szirt@health.nsw.gov.au*

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	*Research Ethics and Governance*
Position	*Research Officer*
Telephone	*(02) 8797 7605*
Email	SESLHD-RSO@health.nsw.gov.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	*WSLHD Human Research Ethics Committee*
Telephone	*02 8890 9007*
Email	*Wslhd-researchoffice@health.nsw.gov.au*

Consent Form

Title	Australia New Zealand Spontaneous Coronary Registry
Short Title	*ANZ-SCAD Registry*
Project Sponsor	*The University of Sydney, Australia*
Coordinating Principal Investigator/ Principal Investigator	*Associate Professor Sarah Zaman*
Associate Investigator(s)	*Dr. Richard Szirt*
Location	**St. George Hospital**

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I acknowledge that any regulatory authorities may have access to my medical records **specifically related** to this project to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

I understand that I will be given a signed copy of this document to keep.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to St. George Hospital concerning my condition and treatment for the purposes of this project. I understand that such information will remain confidential.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation

Title	Australia New Zealand Spontaneous Coronary Registry
Short Title	*ANZ-SCAD Registry*
Project Sponsor	*The University of Sydney, Australia*
Coordinating Principal Investigator/ Principal Investigator	*Associate Professor, Sarah Zaman*
Associate Investigator(s)	*Dr. Richard Szirt*
Location	*St. George Hospital*

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *St. George Hospital.*

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Supplementary table 1 - Univariable analysis of determinants of major adverse cardiovascular events

Univariable analysis		
Variable	**Hazard ratio (95% confidence interval)**	**P value**
Age	1 (0.99–1)	0.12
Female sex	1.6 (0.75–3.4)	0.23
Number of pregnancies	1 (0.7–1.5)	0.92
Family history premature CAD	0.78 (0.41–1.5)	0.45
Previous MI	1.6 (0.67–3.7)	0.3
Hypertension	1.1 (0.64–1.9)	0.7
Diabetes	2.1 (0.5–8.5)	0.31
Dyslipidaemia	1.1 (0.57–2.1)	0.8
Previous stroke	3.7 (1.2-12)	0.027*
Atrial fibrillation	4.5 (1.1–19)	0.039*
Fibromuscular dysplasia	2.1 (1–4.3)	0.047*
History of depression	2 (1.1–3.7)	0.024*
PCI performed	1.1 (0.5–2.3)	0.85

Conservative care	0.93 (0.44–2)	0.85
Coronary tortuosity	1.1 (0.78-1.5)	0.67
Left ventricular ejection fraction	1.2 (0.73-2.1))	0.44
STEMI	1.1 (0.67-2)	0.61
Proximal location of dissection	0.85 (0.39-1.9)	0.7
TIMI flow 1 or less	1.2 (0.65-2.1)	0.6
Type 2A SCAD	0.99 (0.58-1.7)	0.96
Multivessel SCAD	1 (0.44-2.4)	0.95
No antiplatelet	1.3 (0.32–5.3)	0.72
Single antiplatelet therapy Aspirin Clopidogrel	0.86 (0.47–1.5) 0.7 (0.36–1.3) 2.1 (0.74-5.8)	0.6 0.28 0.16
Dual antiplatelet therapy Aspirin + clopidogrel Aspirin + ticagrelor	1.1 (0.63 – 2) 0.7 (0.4 – 1.2) 1.6 (0.94 – 2.8)	0.7 0.22 0.085
Oral anticoagulation	2.9 (1.3–6.9)	0.013 *
Statin	1.1 (0.67–2)	0.62
ACEI or ARB	1.2 (0.7–2)	0.54
Beta-blocker	1.4 (0.71–2.8)	0.32

Mode of recruitment (prospective vs retrospective)	0.4 (0.23-0.80)	0.008 *

ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, PCI=percutaneous coronary intervention, SCAD=spontaneous coronary artery dissection, STEMI=ST-elevation myocardial infarction, TIMI=thrombolysis in myocardial infarction. Asterisk indicates p values of statistical significance.

Ticagrelor as single antiplatelet therapy was not included as the model failed to converge due to no events.

Supplementary table 2 - Univariable analysis of determinants of SCAD recurrence

Variable	**Hazard ratio (95% confidence interval)**	**P value**
Age	1 (0.96–1)	0.85
Female sex	0.33 (0.045–2.4)	0.28
Number of pregnancies	1 (0.56–1.9)	0.95
Family history of premature CAD	0.63 (0.24–1.7)	0.35
Previous MI	1.4 (0.43–4.7)	0.57
Hypertension	0.93 (0.42–2)	0.85
Dyslipidaemia	0.88 (0.33–2.3)	0.79
Previous stroke	5.3 (1.3-22)	0.024 *
Fibromuscular dysplasia	4.1 (1.7-9.9)	0.002 *

History of depression	2 (0.87–4.8)	0.1
PCI performed	0.45 (0.11–1.9)	0.28
Conservative care	2.2 (0.52–9.4)	0.28
Coronary tortuosity	1.2 (0.77-1.9)	0.42
Left ventricular ejection fraction	1 (0.5-2.2)	0.91
Single antiplatelet therapy	0.65 (0.26–1.6)	0.34
Aspirin	0.62 (0.24–1.6)	0.33
Clopidogrel	1.1 (0.15–8)	0.94
Dual antiplatelet therapy	1.8 (0.73–4.4)	0.21
Aspirin + clopidogrel	0.59 (0.26–1.3)	0.21
Aspirin + ticagrelor	2.6 (1.3–5.5)	0.01 *
Statin	0.86 (0.42–1.8)	0.7
ACEI or ARB	1.1 (0.51–2.2)	0.86
Beta-blocker	0.94 (0.4-2.2)	0.9

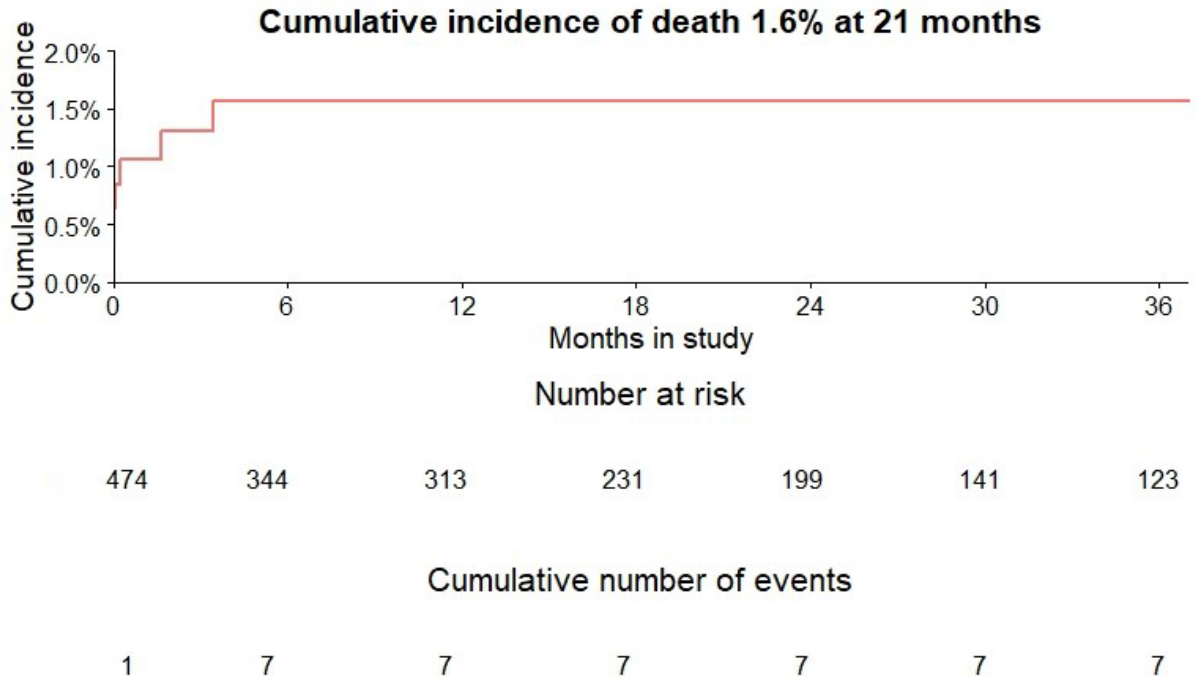
ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, PCI=percutaneous coronary intervention, SCAD=spontaneous coronary artery dissection. Asterisk indicates p values of statistical significance.

Diabetes, no antiplatelet, ticagrelor as single antiplatelet therapy, and anticoagulation were not included as the model failed to converge due to no events.

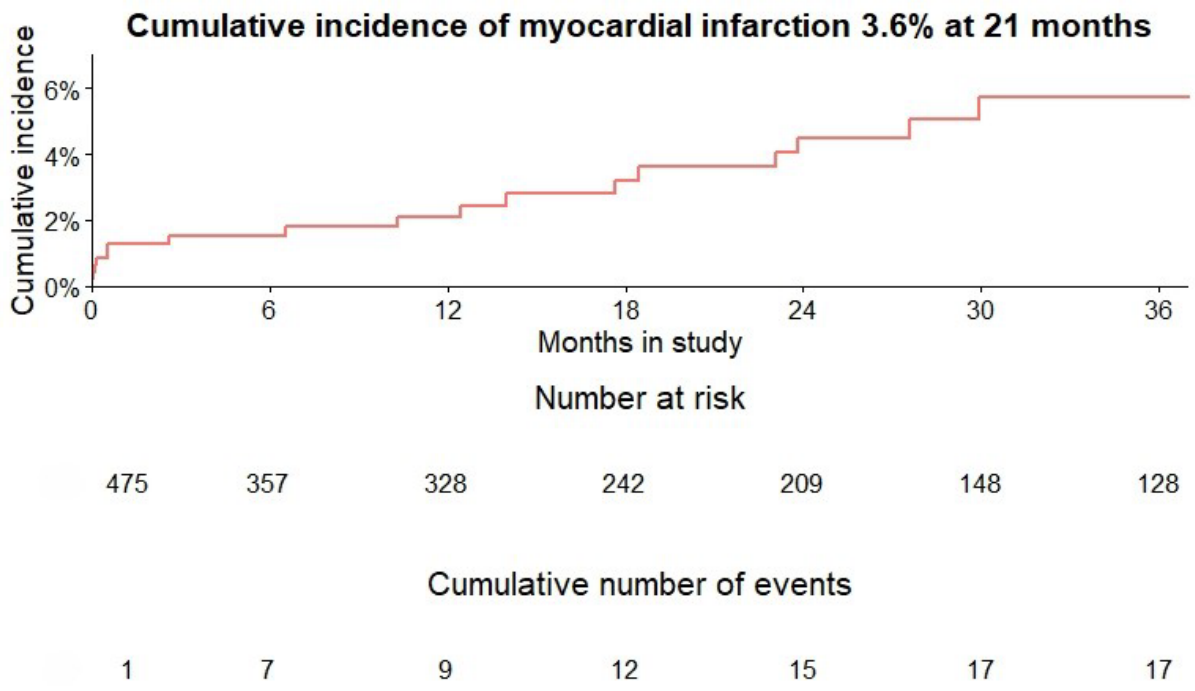
Supplementary table 3 – Correlation between fibromuscular dysplasia and history of stroke

	Previous stroke	No previous stroke	P value
Fibromuscular dysplasia	1	55	0.56
No fibromuscular dysplasia	6	443	

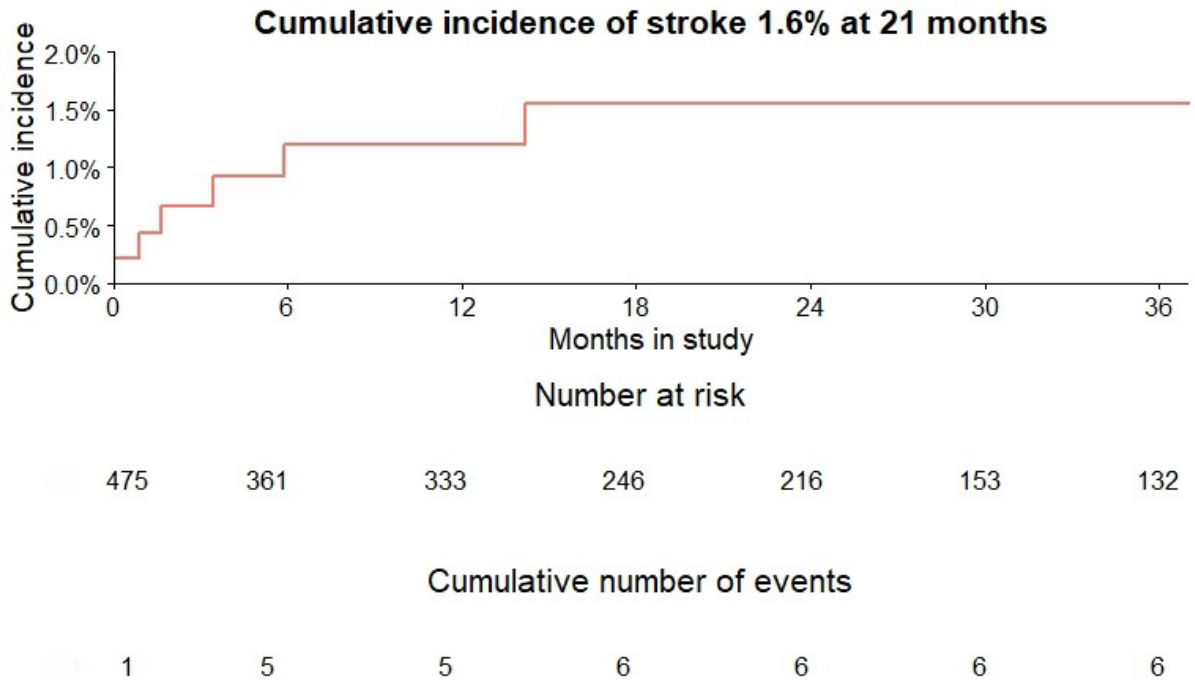
Supplementary figure 1 – Cumulative incidence of death



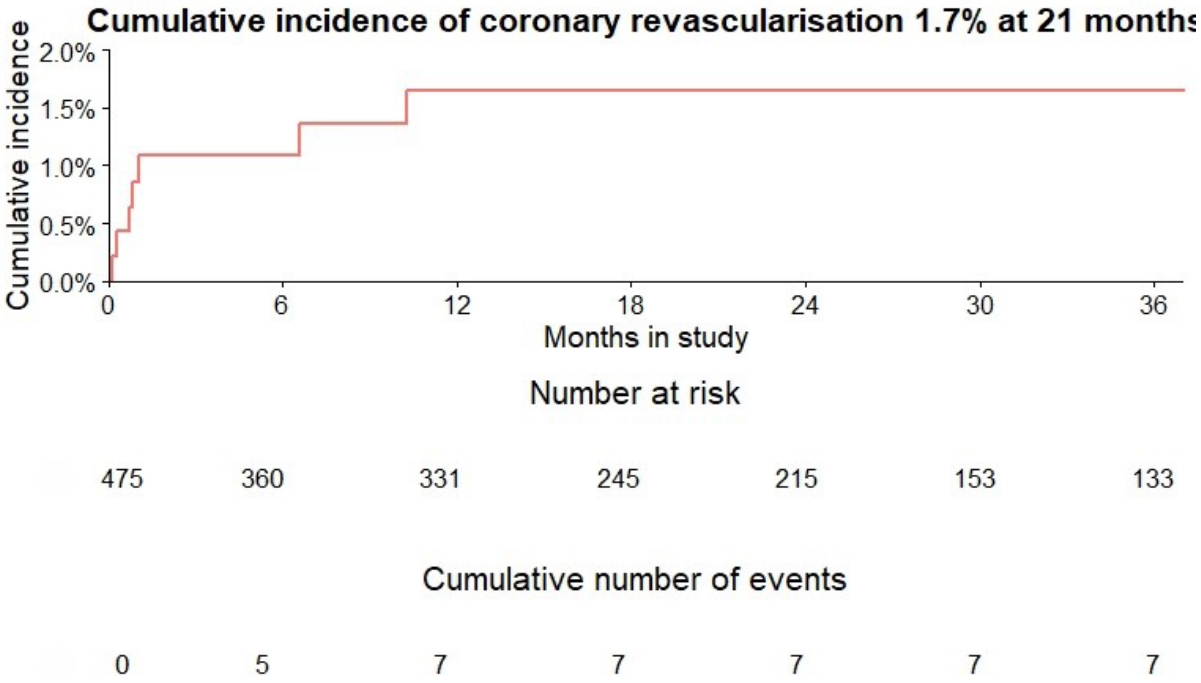
Supplementary figure 2 - Cumulative incidence of myocardial infarction



Supplementary figure 3 – Cumulative incidence of stroke



Supplementary figure 4 - Cumulative incidence of coronary artery revascularisation



Chapter 5: Supplementary materials for paper 3

Table 1 - Search queries

Database	Search query	Date	Results
MEDLINE	1 - spontaneous coronary artery dissection.mp. 2 - spontaneous coronary dissection.mp. 3 - 1 OR 2	16/06/2022	1528
EMBASE	spontaneous coronary artery dissection OR spontaneous coronary dissection	15/06/2022	2297
SCOPUS	TITLE-ABS-KEY ("spontaneous coronary artery dissection") OR TITLE-ABS-KEY ("spontaneous coronary dissection")	16/06/2022	1577
CINAHL	S1 - spontaneous coronary artery dissection S2 - spontaneous coronary dissection S3 - S1 OR S4	16/06/2022	645

Table 2 - PRISMA checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Abstract	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6-7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	7-8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify	7-8

Section and Topic	Item #	Checklist item	Reported on page #
		the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8
Study characteristics	17	Cite each included study and present its characteristics.	21-24
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplemental Table 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	32-33
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	32-33
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplemental Table 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	10-11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10
	23b	Discuss any limitations of the evidence included in the review.	11
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	12
Competing interests	26	Declare any competing interests of review authors.	12
Availability of data, code and other	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

Section and Topic	Item #	Checklist item	Reported on page #
materials			

Table 3 – Risk of bias assessments using New Castle-Ottawa Scale

Author	Year	Selection 1	Selection 2	Selection 3	Selection 4	Comparability	Outcome 1	Outcome 2	Outcome 3
Daoulah	2021	*	*		*		*	*	
McGrath-Cadell	2016	*	*	*	*		*	*	*
Rashid	2016	*		*			*	*	*
Adams	2018		*		*	*	*	*	*
Tarr	2022	*		*		*	*	*	
Chou	2016			*			*	*	
Bouchard	2021			*			*		
Inohara	2021	*	*	*	*	* *	*	*	
Solomonica	2020	*	*	*	*		*	*	
Saw	2019	*	*	*	*	*	*	*	

Sun	2019	*		*		*	*	*	
Hui	2020	*	*	*	*	* *	*	*	
Chang	2022	*	*	*			*	*	*
Mortensen	2009	*	*	*			*	*	*
Combaret	2021	*	*	*			*	*	
Panneerselvam	2017	*	*	*			*	*	*
Almasi	2022	*	*	*	*		*	*	
Lettieri	2015	*	*	*	*		*	*	
Antonutti	2021	*	*	*	*	*	*	*	
Solinas	2022	*	*	*			*	*	
Cerrato	2021	*	*	*	*		*	*	*
Nakashima	2016	*	*	*	*		*	*	*
Nishiguchi	2017		*	*			*	*	

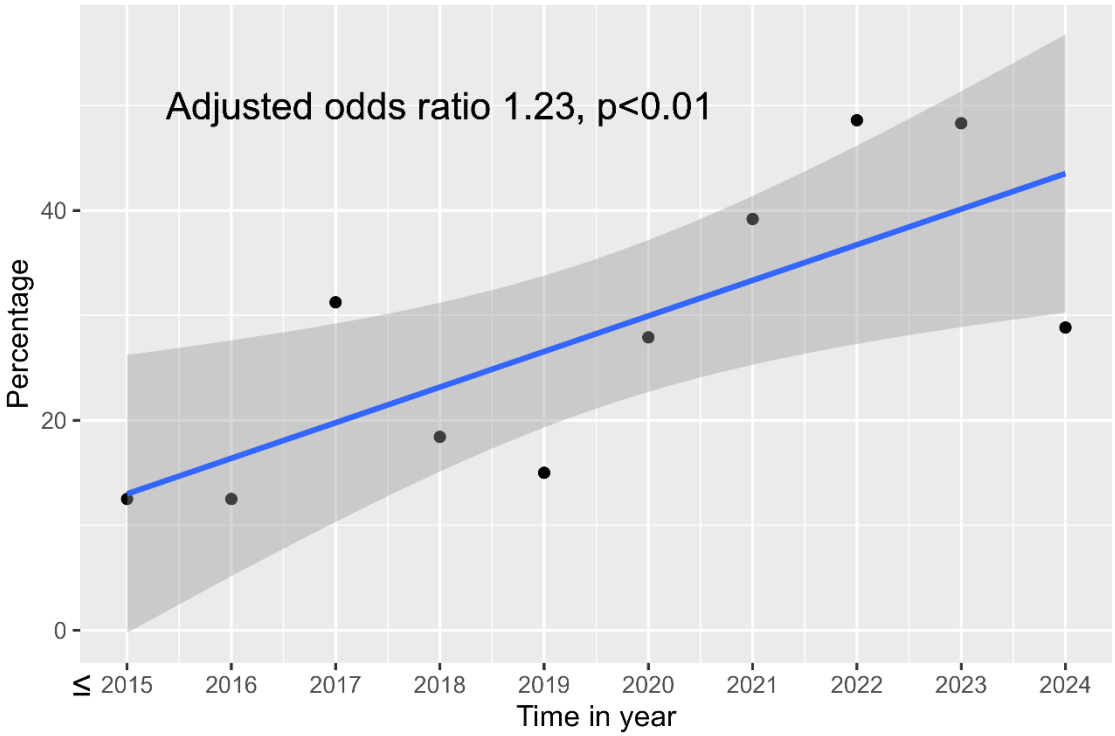
Inohara	2020	*	*	*	*		*	*	
Inoue	2021	*	*	*			*	*	*
Kim	2021	*	*	*	*		*	*	*
McAlister	2021	*	*	*	*		*	*	*
Romero-Rodriguez	2010	*	*	*			*	*	*
Alfonso	2012	*	*	*	*		*	*	
Alfonso	2012	*	*	*	*		*	*	*
Camacho Freire	2019	*	*	*	*	* *	*	*	*
Bastante	2020	*	*	*	*		*	*	*
Macaya	2020	*	*	*	*	* *	*	*	*
Mori	2020	*	*	*	*	* *	*	*	

Garcia-Guimaraes	2022	*	*	*	*	*	*	*	*
Murugiah	2022	*	*	*	*	* *	*	*	
Wilander	2022	*	*	*	*		*	*	*
Seidl	2021	*	*	*	*		*	*	
Smaardijk	2020	*		*			*	*	
Carss	2020	*		*		*	*	*	
Androulakis	2022			*		* *	*	*	
Kotecha	2021	*	*	*	*	*	*	*	*
De Maio Jr	1989			*			*	*	*
Liang	2014	*		*			*	*	
Wagers	2018							*	
Clare	2019	*		*	*	*	*	*	*

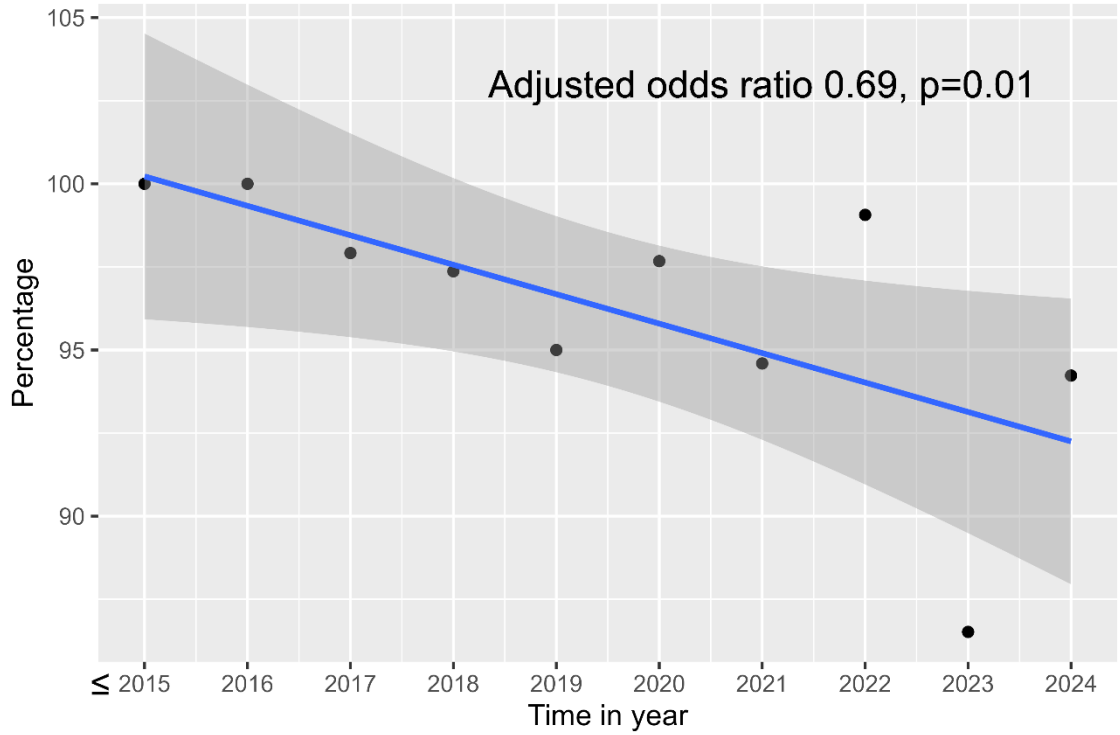
Sharma	2019	*		*			*	*	
McNair	2020	*	*	*	*		*	*	*
Turley	2020	*		*			*	*	
Chen	2021	*	*	*	*	*	*	*	*
Baechler	2022	*		*			*	*	
Johnson	2022	*		*			*		
White Solaru	2019			*	*		*		*

Chapter 6: Supplementary materials for paper 4

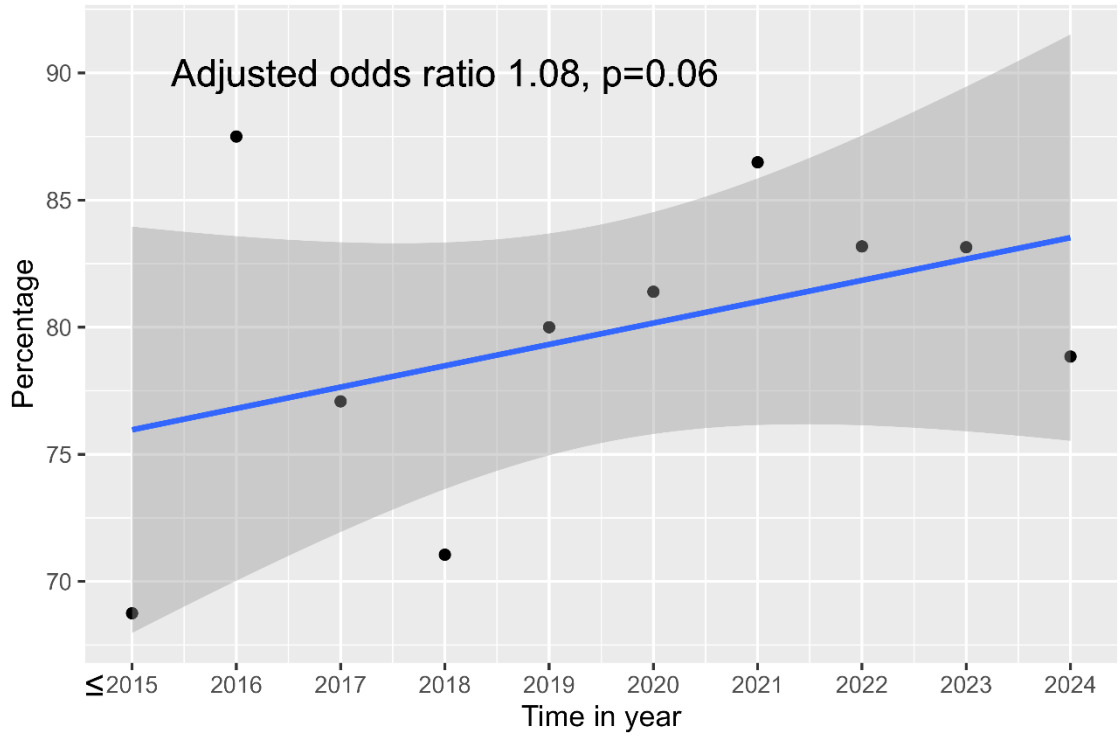
Supplementary figure 1 – Percentage of SCAD survivors who received all four key recommendations of at least one antiplatelet, beta blocker therapy, FMD screening and referral to cardiac rehabilitation, over time



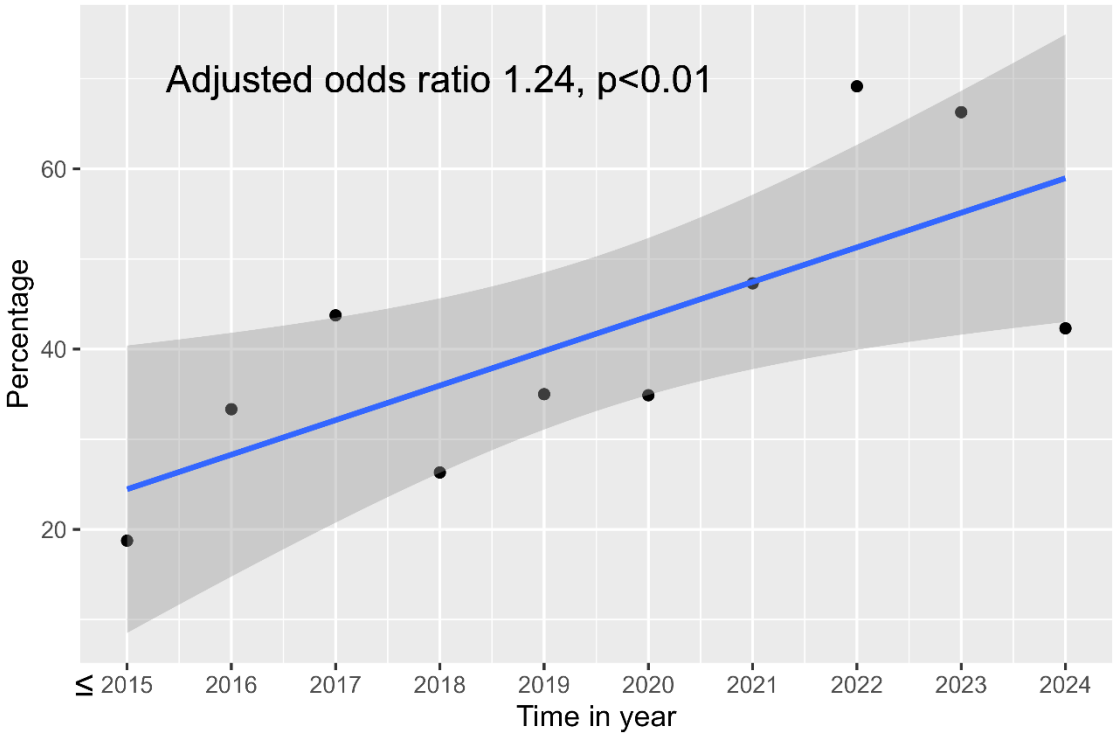
Supplementary Figure 2 – Percentage of patients receiving at least one antiplatelet agent over time



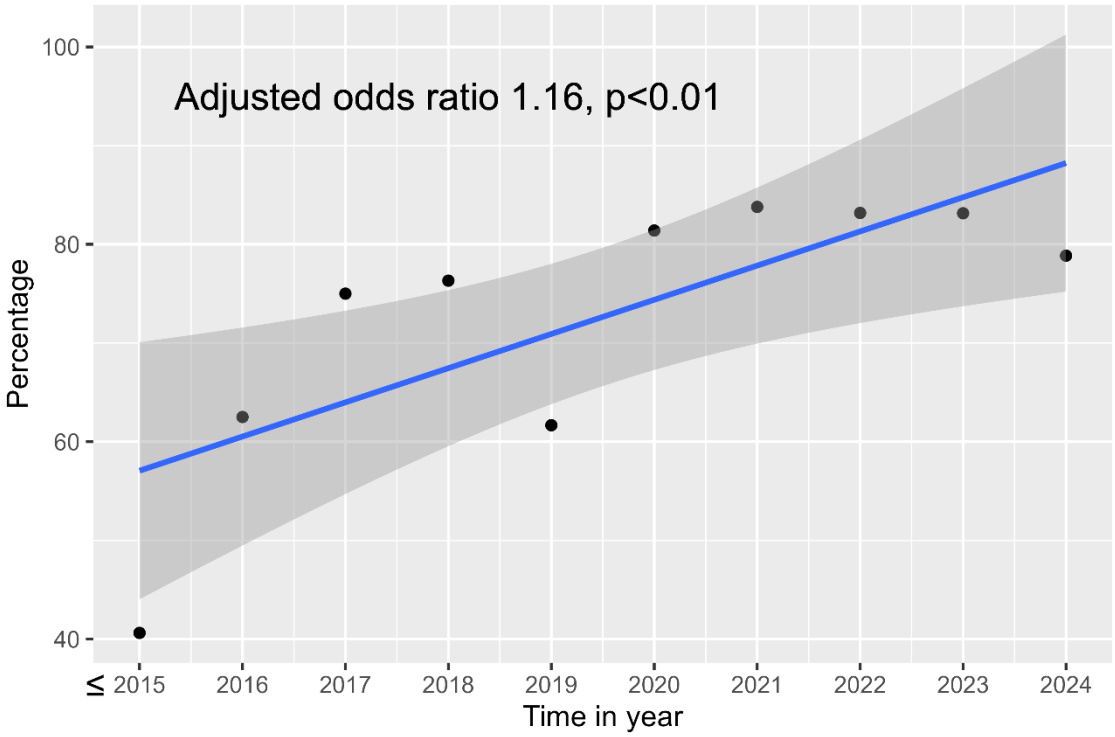
Supplementary Figure 3 – Percentage of patients receiving beta-blockers over time



Supplementary Figure 4 – Percentage of patients screened for FMD over time



Supplementary Figure 5 – Percentage of patients referred to cardiac rehabilitation over time



Questionnaire

Chapter 7: Supplementary materials for paper 5

Please complete the survey below.

Thank you!

You are invited to take part in this research project, "Spontaneous Coronary Artery Dissection (SCAD): Australian patients' perspectives on quality of care, quality of life and priorities for future research". This is because you have been diagnosed with SCAD and you are living in Australia. The research project aims to obtain information about participatnts' quality of care, quality of life and priorities for future research.

Participant Information Sheet/Consent Form is available through the below link. It tells you about the research project. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

[Attachment: "PIS WSLHD V1 020522.pdf"]

Do you agree to participate in this survey? ◯ Yes ◯ No

---

1 Your age

_____

---

2 Your gender

◯ Male
◯ Female
◯ Other

---

3 Your postcode at the time of SCAD diagnosis

_____

---

4 Your Ethnicity

◯ Aboriginal &/or Torres Strait Islander
◯ Caucasian/ white (including European, Anglo-Celtic)
◯ Asian (Far-East, South East Asia including Cambodia, China, Japan, Korea, Philippines, Thailand, Vietnam)
◯ Southern Asian (including INdia, Afghanistan, Pakistan, Bangladesh, Nepal, bhutan, Maldives Sri Lanka)
◯ African (including African American)
◯ Maori
◯ Pacific Peoples (Islander)
◯ Middle Eastern and Northern Africa (Lebanese, Iranian, Egyptian, Syrian, Moroccan, Algerian, etc)
◯ Other

Please specify

_____

5 Your past medical history, at the time of your SCAD diagnosis (use the first episode if you have had multiple SCAD episodes) - Please tick all that apply.

- ☐ High blood pressure (or taking blood pressure medication)
- ☐ High blood cholesterol or taking cholesterol lowering medications
- ☐ Diabetes
- ☐ Current smoker or previous cigarette smoker
- ☐ Family history of stroke or heart attack among first-degree relatives (i.e., parents, siblings or children)
- ☐ Autoimmune conditions/ Inflammatory condition/ Fibromuscular dysplasia /Connective tissue disease
- ☐ Other

Please specify _____

6 Total number of SCAD episodes

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ >3

7 Approximate time of FIRST SCAD episode (please enter below)

Month

- ◯ January
- ◯ February
- ◯ March
- ◯ April
- ◯ May
- ◯ June
- ◯ July
- ◯ August
- ◯ September
- ◯ October
- ◯ November
- ◯ December

Year _____

Approximate time of MOST RECENT SCAD episode (please enter below)

Month

- ◯ January
- ◯ February
- ◯ March
- ◯ April
- ◯ May
- ◯ June
- ◯ July
- ◯ August
- ◯ September
- ◯ October
- ◯ November
- ◯ December

Year _____

If you have had more than one episode of SCAD, please answer the following questions in regards to your first SCAD diagnosis.

8 What were the symptoms? Please tick all that apply.

- ☐ Chest pain
- ☐ Shortness of breath
- ☐ Nausea and/ or vomiting
- ☐ Arm pain
- ☐ Neck or throat pain
- ☐ Dizziness or light-headedness
- ☐ Fainting or loss of consciousness
- ☐ Other

Please specify _____

9 From the start of your symptoms, how long did it take you to go to hospital/ emergency department /seek medical care?

- ◯ < 3 hours
- ◯ 3-12 hours
- ◯ 12-24 hours
- ◯ 1-2 days
- ◯ 3+ days
- ◯ Uncertain/ not applicable

10 From the time that you arrived at a hospital/ emergency department / other medical facility, how long did it take for the medical team to consider or reach a diagnosis of SCAD?

- ◯ It was immediatelyconsidered (i.e. within hours)
- ◯ 1 day or less
- ◯ 2-3 days
- ◯ 3+ days
- ◯ It was't diagnosed at the time of myhospital admission/ presentation
- ◯ Uncertain/ not applicable

11 Please rate the following statement: "In the Emergency Department, my symptoms were treated seriously as a heart attack."

- ◯ Strongly agree
- ◯ Agree
- ◯ Neither agree nor disagree
- ◯ Disagree
- ◯ Strongly disagree

12 Can you rate the overall quality of care you received when in hospital for your first episode of SCAD?

With 10 being the best care, and 1 being incredibly poor care.

1 - Incredibly poor care | 5 | 10 - Best care

(Place a mark on the scale above)

The above question is ◯ Not applicable

13 Can you rate how knowledgeable you felt the Emergency Department team were in regards to SCAD? (doctors/nurses who treated you in Emergency).

1 - Not knowledgeable at all | 5 | 10 - Very knowledgeable

(Place a mark on the scale above)

The above question is ◯ Not applicable

14 Can you rate how knowledgeable you felt the cardiology team looking after you on the ward was in regards to SCAD? (cardiologists/ doctors /nurses on the ward).

1 - Not knowledgeable at all | 5 | 10 - Very knowledgeable

(Place a mark on the scale above)

The above question is ◯ Not applicable

15 In the first year after your diagnosis with SCAD, did you receive any of the following treatments? (Tick all that apply)

- ☐ Aspirin
- ☐ Second blood thinner - e.g.,clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), ...
- ☐ Beta-blocker - e.g., metoprolol, bisoprolol, atenolol, carvedilol, labetalol, ...
- ☐ Statin or other cholesterol lowering medications
- ☐ Stent or balloon to the heart artery (blood vessel)
- ☐ Coronary artery bypass surgery
- ☐ Other

Please specify

_____

16 How satisfied are you with the SCAD information provided by your treating doctor?

- ◯ Completely satisfied
- ◯ Satisfied ◯ Neutral
- ◯ Dissatisfied ◯ Completely dissatisfied

17 Apart from the information provided by your treating doctor, did you seek further information regarding SCAD?

- ☐ Internet search
- ☐ Family/ friends
- ☐ Support groups
- ☐ Other

Please specify

_____

18 What source of information about SCAD is the most useful to you (including your treating doctor)?

_____

Have you been referred to a cardiac rehabilitation program?

- ◯ Yes
- ◯ No

What was your level of engagement in the cardiac rehabilitation program

- ◯ I have fully completed the program.
- ◯ I am still in the program.
- ◯ I attended the program but did not fully completed it
- ◯ I did not attend the program at all

What kind of cardiac rehabilitation program did you attend?

- ◯ A general cardiac rehabilitation program
- ◯ A SCAD-specific cardiac rehabilitation program

Would you be interested in attending a SCAD-specific cardiac rehabilitation program?

- ◯ Yes
- ◯ No
- ◯ Not sure

Please rate your overall experience with the cardiac rehabilitation program that you attend/ attended

- ◯ Very helpful
- ◯ Helpful
- ◯ Somewhat helpful
- ◯ Neutral
- ◯ Somewhat unhelpful
- ◯ Unhelpful
- ◯ Very unhelpful

	What are/were the barriers to you attending a cardiac rehabilitation program?	☐ Time - I don't have time to go to the program. ☐ Distance - there is no cardiac rehab centre near my home. ☐ The program - the activities are/were not suitable for me. ☐ Fellow participants - I feel/felt uncomfortable as the other patients are/were dissimilar to myself ☐ Other reason(s)
	Please specify	_____
19	Following your first diagnosis with SCAD, did you see a cardiologist (heart specialist) after discharge from hospital?	◯ Yes ◯ No ◯ Not sure
20	Do you know that fibromuscular dysplasia (FMD) is a condition associated with SCAD?	◯ Yes ◯ No ◯ Not sure
21	Have you been screened for FMD?	◯ Yes ◯ No ◯ Not sure
	Was FMD diagnosed after the screening?	◯ Yes ◯ No ◯ Not sure
22	Have you ever been diagnosed with a mental health illness (such as depression, anxiety or post traumatic stress syndrome), and what is the timing of diagnosis with regards to SCAD?	◯ Yes, prior to my diagnosis with SCAD ◯ Yes, after my diagnosis with SCAD ◯ No, I have never been diagnosed with a mental health illness
	Which mental health condition have you been diagnosed with?	☐ Depression ☐ Anxiety ☐ Post Traumatic Stress Disorder (PTSD) ☐ Other
	Please specify	_____
23	In the first 2 years after your first diagnosis with SCAD did you return to any emergency department or were you admitted to hospital due to recurrent chest pain or SCAD-related symptoms?	◯ Yes ◯ No
	How many times?	_____

Under each heading, please click ONE box that best describe your health TODAY.

24 Mobility

◯ I have no problems in walking around.
◯ I have some problems in walking around.
◯ I am confined to bed

25 Personal Care

◯ I have no problems with personal care.
◯ I have some prolems washing or dressing myself.
◯ I am unable to wash or dress myself.

26 Usual Activities (e.g. work, study, housework, family or leisure activities)

◯ I have no problems with performing my usual activites.
◯ I have some problems with performing my usual activities.
◯ I am unable to perform my usual activities.

27 Pain/ Discomfort

◯ I have no pain or discomfort.
◯ I have moderate pain or discomfort.
◯ I have extreme pain or dicomfort.

28 Anxiety/ Depression

◯ I am not anxious or depressed.
◯ I am moderately anxious or depressed.
◯ I am extremely anxious or depressed.
(It is advisable that you seek medical attention if you feel depressed or anxious.)

29 We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Please click on the scale to indicate how your health is TODAY.

0 - The worst health you can imagine | 50 | 100 - The best health you can imagine

(Place a mark on the scale above)

The following is a list of activities that people often do during a normal week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had due to chest pain, chest tightness or anginal attacks over the past 4 weeks.

30 Walking indoors on level ground

- ◯ Extremely limited
- ◯ Quite a bit limited
- ◯ Moderately limited
- ◯ Slightly limited
- ◯ Not at all limited
- ◯ Limited for other reasons or did not do the activity

31 Gardening, vacuuming or carrying groceries

- ◯ Extremely limited
- ◯ Quite a bit limited
- ◯ Moderately limited
- ◯ Slightly limited
- ◯ Not at all limited
- ◯ Limited for other reasons or did not do the activity

32 Lifting or moving heavy objects like furniture, or lifting children

- ◯ Extremely limited
- ◯ Quite a bit limited
- ◯ Moderately limited
- ◯ Slightly limited
- ◯ Not at all limited
- ◯ Limited for other reasons or did not do the activity

Over the past 4 weeks, on average, how many times have you had chest pain, chest tightness or anginal attacks?

33 I have had chest pain, chest tightness or anginal attacks...

- ◯ 4 or more times per day
- ◯ 1-3 times per day
- ◯ 3 or more times per week but not everyday
- ◯ 1-2 times per week
- ◯ Less than once a week
- ◯ None over the past 4 weeks

Over the past 4 weeks, on average, how many times have you had to use nitrolingual spray, or put an anginine, or isordil tablet under the tongue, to relieve chest pain, chest tightness, or anginal attacks?

34 I have used them...

- ◯ 4 or more times per day
- ◯ 1-3 times per day
- ◯ 3 or more times per week but not everyday
- ◯ 1-2 times per week
- ◯ Less than once a week
- ◯ None over the past 4 weeks

35 Over the past 4 weeks, how much has your chest pain, chest tightness or anginal attacks limited your enjoyment of life?

- ◯ It has extremely limited my enjoyment of life
- ◯ It has limited my enjoyment of life quite a bit
- ◯ It has moderately limited my enjoyment of life
- ◯ It has slightly limited my enjoyment of life
- ◯ It has not limited my enjoyment of life at all

36 If you had to spend the rest of your life with your chest pain, chest tightness or anginal attacks the way it is at the moment, how would you feel about this?

- ◯ Not satisfied at all
- ◯ Most dissatisfied
- ◯ Somewhat satisfied
- ◯ Mostly satisfied
- ◯ Completely satisfied

37 From your perspective, what do you think is the priority for research into SCAD?

- ☐ Research into the best medical treatments for SCAD (e.g. determining if aspirin or other blood thinners are needed, who should receive stents or surgery, and if medications like beta blockers or cholesterol lowering tablets are needed)
- ☐ Improving understanding of the genetic basis for SCAD, ie understanding if other family members might be at risk
- ☐ Understanding the underlying reason for SCAD, i.e understanding why the heart artery tears in the first place, determining who is most at risk
- ☐ Improving the quality of medical care for SCAD ie educating doctors and nurses to recognise SCAD, improving diagnosis of SCAD
- ☐ Improving the public awareness of SCAD ie. Ensuring other people with symptoms of SCAD know to come to emergency in the instance of chest pain, despite perhaps not having usual heart disease risk factors

38 This is the last question of the survey: can you please tell us what YOU think researchers should focus on in SCAD?

_____

If you would like to receive feedback about the results of this survey, please click on submit and follow the link on the next page.

Quality of care, quality of life and research priorities of patients with Spontaneous Coronary Artery Dissection (SCAD) in Australia.

Background

Spontaneous coronary artery dissection (SCAD) is a relatively uncommon medical condition which affects mostly young women and can cause acute coronary syndrome. Once considered to be a rare disease, SCAD is now known to be the cause of up to 10 % of all acute coronary syndrome and about a third of myocardial infarction in women under the age of 50.[1-6]

The exact pathophysiology of SCAD remains unestablished, as is the optimal management for SCAD. This lack of information about a life-threatening condition may result in dissatisfaction, anxiety and stress among SCAD survivors. Previous studies have demonstrated significant prevalence of mental health issues in this group of patients[7-9].

Some clinicians manage SCAD similarly to atherosclerotic acute coronary syndrome, with antiplatelets and statins. However, there is little evidence to support the use of the former and the latter may even cause harm. [1, 2, 10]. Cardiac rehabilitation has been demonstrated to be a safe intervention that may improve the physical and psychological well-being of SCAD patients. [11-16] Despite this, the rate of referral to and participation in cardiac rehabilitation remains relatively low. [17, 18]

As SCAD was thought to be a rare condition, many clinicians may have low levels of suspicion or awareness. In addition, the fact that SCAD patients are likely to be young females without traditional risk factors for cardiovascular disease may contribute to delays in diagnosis and management. Many SCAD survivors reported that their symptoms were not taken seriously or even were dismissed by the Emergency staff. [19, 20]

A few extra coronary arteriopathies have been found to be associated with SCAD, most commonly fibromuscular dysplasia (FMD), [4, 21-27] a condition affecting medium-size arteries, predisposing to the formation of aneurysms or dissections. International guidelines have advocated for the screening of FMD [2, 5]. There is no data about the uptake of this recommendation in Australia, however anecdotal experience suggests that it is likely to be low.

Aims

This project aims to explore the experience of SCAD survivors with regards to their medical quality of care and the effects that this condition causes on their well-being and quality of life.

The project has three main aims:

1. To explore participants' perception on the quality of the care they received.
    - Time from symptom onset to diagnosis
    - Participants' experience in the Emergency Department
    - Participants' perception on the adequacy of information on SCAD that was provided by their treating doctor
    - If the participant received screening for associated conditions with SCAD, e.g. fibromuscular dysplasia
    - If the participant was referred to or attended cardiac rehab
2. To assess participants' quality of life and its correlation with the recurrence of symptoms and mental health disorders
3. To identify participants' priorities for future research.

Objectives

1. To assess the performance of our medical care system with regards to SCAD as seen from the consumer perspective
2. To assess the quality of life of SCAD survivors and its determinants
3. To identify consumer's priorities for future research

Hypothesis

We hypothesize that many participants with SCAD have significant delays in their diagnosis and treatment and this may correlate with their age and the number of traditional cardiovascular risk factors that they have. Some participants may experience dismissal treatment in the Emergency Department. SCAD survivors have lower quality of life compared to population's average and this correlates with the recurrence of their symptoms.

Method

Participants

Participants will be invited to participate in an online survey from two established cohorts:

- By emailing a link of the online survey via the SCAD Research Incorporation Australia contact list of SCAD survivors: this is a not-for-profit philanthropic organization that is run by a SCAD survivor, and has regular meet ups and fundraising events.
- By posting a link of the online survey via the Australian SCAD Survivors Facebook page (935 members, closed/private group of only SCAD survivors)

The online link will be sent via email (with two reminder emails) by the director of the SCAD Research Inc Australia (the researchers will not have direct access to participants' email addresses). The online link will be posted by a member of the Australian SCAD Survivors Facebook Page (the researchers do not have direct access to the page as it is only for SCAD Survivors) with two subsequent reminder posts to encourage participation.

Consent

- Participants' involvement in the survey will be completely voluntary
- Participants' consent will be assumed if they follow the link (which includes viewing the PiS) and complete and submit the survey
- Participants' responses will be completely anonymous, with no identifiable information recorded (including no name, email or other contact details recorded) and only published in the form of pooled data

Surveys/Data

- The surveys are shown in Attachment – "Participant Surveys"
- The surveys include:
  - Demographic data (age, gender, ethnicity)
  - Geographical data (Postcode)
- The majority of the data collected will be categorical data with some responses given using a 5-point Likert scale.

Database Creation & Data Security

- An online database using REDcaps will be used to create the surveys and enable secure housing of the responses.
  - the REDcap database is a secure online database housed within the University of Sydney
  - all data management and analysis will be supervised by the Principal Investigator
- Only investigators on the ethics application have password-secure access to this database.
- Data obtained through survey participation will be completely anonymous, as no identifying data is collected, and only pooled data will be reported and/or published.
- At the end of the study, the data will be owned by the University of Sydney and retained in a secure online form within the RedCap database.
- All data will be retained for 7 years following completion of the study in an electronic format only. At the end of the 7 years the redcap database will be deleted.

Data Analysis

- Statistical significance has been pre-determined as a p-value of < 0.05
- Statistical analysis will be performed using SPSS (Statistical Package for the Social Sciences, IBM)

- All analysis and interpretation of the data will be conducted by the team of investigators mentioned on the ethics application, under the supervision of the Principal Investigator. All analyses will be discussed with the entire team of investigators.

Investigators

- Principal investigator: Associate Professor Sarah Zaman, Principal Research Fellow, Westmead Applied Research Centre, Faculty of Medicine and Health (FMH), The University of Sydney
- Investigator: Dr Quan Dang, PhD Candidate, Faculty of Medicine and Health (FMH), The University of Sydney

Funding

This is an investigator-initiated study conducted via online surveys, with no funding. Sponsor for this study is The University of Sydney

Outcome

This survey-based study will provide valuable data on patient's perception on quality of care for SCAD survivors in Australia. The data could then be compared with similar surveys worldwide to help identify the strengths and weaknesses of our current health care system. It will also provide information on patient's priorities to guide future research into SCAD.

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Quan Dang

From: no_reply@regis.health.nsw.gov.au
Sent: Thursday, 4 August 2022 7:30 PM
To: sarah.zaman@sydney.edu.au
Cc: Quan Minh Dang
Subject: 2022/PID00927 - 2022/ETH00826: Application HREA - Approved

Date of Decision Notification: 04 Aug 2022

Dear Sarah Zaman,

Thank you for submitting the following Human Research Ethics Application (HREA) for HREC review;

2022/PID00927 - 2022/ETH00826: Spontaneous Coronary Artery Dissection: Australian patients' perspectives on quality of care, quality of life and priorities for future research.

The Application has been reviewed by a subcommittee of members of the Scientific Advisory Committee (SAC) and the Human Research Ethics Committee (HREC). The project was determined to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was APPROVED.

This email constitutes ethical and scientific approval only. This project cannot proceed at any site until separate research governance authorisation has been obtained from the Institution at which the research will take place.

This project has been Approved to be conducted at the following sites:

- Westmead Hospital

The following documentation was reviewed and is included in this approval:

1. HREA Application
2. Protocol, version 2 dated 23 June 2022
3. Participant information and Consent Form, version 3 dated 15 July 2022
4. Survey Advertisement – Email, version 1 dated 3 May 2022
5. Survey Advertisement - Social Media, version 1 dated 3 May 2022
6. Questionnaire, version 1 dated 3 May 2022

Application Documents - (link will only be active for 14 days from the decision date. The approved documents are also available to download from forms section of this project in REGIS)

Participant Information Sheet/Consent Form

Non-Interventional Study - *Adult providing own consent*

Title	Spontaneous Coronary Artery Dissection (SCAD): Australian patients' perspectives on quality of care, quality of life and priorities for future research
Short Title	SCAD survivors survey
Coordinating Principal Investigator/ Principal Investigator	Assoc Prof Sarah Zaman Dr Quan Dang
Location	Online Survey

1. Introduction

You are invited to take part in this research project, SCAD survivors survey. This is because you are an Australian resident who has been diagnosed with SCAD. The research project is aiming to provide information about the quality of care and quality of life of people with SCAD, as well as their priorities for future research.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and research involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether you take part.

If you decide you want to take part in the research project, please answer "Yes" in the next question on the online survey. By clicking on it you are telling us that you:
• Understand what you have read
• Consent to take part in the research project
• Consent to the use of your health information as described.

You may print out this Participant Information Form to keep.

2. What is this study about?

We are conducting a research study about the quality of care and quality of life of Spontaneous Coronary Artery Dissection (SCAD) patients in Australia. Taking part in this study is voluntary.

Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

3. Who is running the study?

The study is being carried out by the following researchers:

- Associate Professor Sarah Zaman, Principal Research Fellow, Westmead Applied Research Centre, Faculty of Medicine and Health (The University of Sydney)
- Dr Quan Dang, PhD Candidate, Faculty of Medicine and Health (The University of Sydney)

Dr Quan Dang is conducting this study as the basis for the degree of Doctor of Philosophy at The University of Sydney.

4. Who can take part in the study?

We are seeking people who were diagnosed with SCAD and who are living in Australia.

You have been invited to take part in this study because you meet the criteria above.

5. What will the study involve for me?

If you decide to take part in this study, you will be asked to participate in an online survey.

- The survey should take about 7-10 minutes to complete.
- You will be asked questions relevant to the quality of care that you received, and the quality of your life, including questions about your mental health history. You will also be asked about your opinion on what should be the focus or priority of future research on SCAD.
- There will be no access to your existing records of information (e.g. medical records)
- There will be no audio/video/photographs/other recording involved
- At this stage, the survey is in English only
- If you would like to receive feedback about the overall results of the survey, there is an option for you to enter your email address after the survey is submitted. Feedback in the form of a brief lay summary will be sent to your email when it is available.

6. Can I withdraw once I've started?

Being in this study is completely voluntary and you do not have to take part.

Your decision will not affect your current or future relationship with the researchers or anyone else at The University of Sydney.

We do not anticipate your decision will affect your relationship with anyone else.

If you decide to take part in the study and then change your mind you can withdraw at any time.

By submitting your survey, you consent to take part in the study. You can withdraw any time before you submit however once your responses are submitted, they cannot be withdrawn. This is because they are anonymous, and we will not be able to tell which one yours is.

7. Are there any risks or costs?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this study.

8. Are there any benefits?

You will not receive any direct benefits from being in the study.

9. What will happen to information that is collected?

By providing your consent, you are agreeing to us collecting information about you for the purposes of this study.

- Any information you provide us will be stored securely and we will only disclose it with your permission, unless we are required by law to release information.

- No third party will have access to your information during or after the study.

- Electronic information will be collected and stored using REDCaps, a secure password-protected, online database housed within the University of Sydney.

- Electronic information will be destroyed after the approved retention period (7 years).

- Data collected as part of the study is not intended to be used for any other purpose (e.g., further research, establishment of a database, submission to a public data repository).

- We are planning for the study findings to be published.

- You will not be individually identifiable in these publications.

10. Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You may enter your email address at the end of the survey if you wish to receive it. This feedback will be in the form of a brief lay summary.

11. What if I would like further information?

When you have read this information, the following researcher/s will be available to discuss it with you further and answer any questions you may have:

Name	Quan Dang
Position	PhD Candidate (University of Sydney)
Email	qdan6570@uni.sydney.edu.au

12. What if I have a complaint or any concerns?

The ethical aspects of this study have been approved by the Human Research Ethics Committee (HREC) of Western Sydney Local Health District according to the *National Statement on Ethical Conduct in Research Involving Humans (2007, updated May 2015).*

If you are concerned about the way this study is being conducted or wish to make a complaint to someone independent from the study, please contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	WSLHD Human Research Ethics Committee
Executive Officer	Kellie Hansen
Telephone	02 8890 9007
Email	Wslhd-researchoffice@health.nsw.gov.au

The approval is for a period of 5 years from the date of this e-mail (04 Aug 2022)

The Committee granted a waiver of the usual requirement of consent for the use of re-identifiable information held by NSW agencies, in line with the State Privacy Commissioner's Guidelines for Research and the Health Records and Information Privacy Act 2002 (NSW) and the Guidelines approved under Section 95/95A of the Privacy Act 1988. If Waiver of Consent

The Coordinating Principal Investigator will:
• provide the HREC with an annual report and the final report when the project is completed at all sites. This will be through the submission of a milestone in REGIS.
• immediately report anything that might warrant review of ethical approval of the project.
• submit proposed amendments to the research protocol, including; the general conduct of the research, changes to CPI or site PI, an extension to HREC approval, or the addition of sites to the HREC before those changes can take effect. This will be through a notification of an amendment in REGIS
• will notify the HREC if the project is discontinued at a participating site before the expected completion date, with reasons provided.

Submission of annual progress/final reports (milestone), amendments and safety reports should be done through the forms provided in REGIS. Guidance on these processes can be found on the REGIS website.

It is noted that the Western Sydney Local Health District Human Research Ethics Committee is constituted in accordance with the National Statement on Human Conduct in Human Research, 2007 (NHMRC).

The processes used by the HREC to review multi-centre research proposals have been certified by the National Health and Medical Research Council.

Please contact us if you would like to discuss any aspects of this process further, as per the contact details below. We look forward to managing this study with you throughout the project lifecycle.

Regards,
WSLHD Research Office

Supplementary table 1 - Participants' research priorities and comments

research_focus
Understanding the trigger for SCAD or best treatment to prevent recurrence
A study to determine if there is a relationship between oral contraceptives and SCAD.
Preventative measures
Why it happens Can it be prevented with screening of arteries
What causes SCAD
Guidelines for blood pressure control so that GPs have a standard to follow, and so that patients can safely titrate their medications (under medical supervision) if necessary. For example, I'm a nurse and my BP 5 weeks post SCAD is 150/100. I'd like to be able to take an extra dose of medication if necessary without having to ring my GP each time.
As above, they are all so very important.
Who is really at risk of another SCAD and whether medication is really necessary to prevent a recurrence, particularly statins. Prior to SCAD, I exercised vigorously and now the medical recommendations have me scared to resume that life which impacts my passion for hiking, particularly in remote areas.
Educating emergency departments, I was initially given tablets of mylanta
The causes of Scad and Educating Cardiologists, G.P.'s, Emergency Dept Doctors, Nurses and Rehab facilities and medical staff about SCAD and the mental health

issues that accompany a diagnosis. Providing educational resources to newly diagnosed patients.
we all have stress in our lives but the research suggests the correlation between this and SCAD is loose at best. Those of us who've had a SCAD want to know how to prevent another one. i've chosen to be on a low dose of an anti-anxiety med and I think it helps reduce my chest pain - I'd like to see some research into this
Understanding why certain people get this and what we can do to prevent it
Would love to know more about the continued yet occasional chest pain post scad
At present I am most interested in more extensive research into medical prevention of SCAD as I dislike taking medications long term due to side effects and do not want to be overprescribed medication which have little sound medical research they will actually help prevent another attack. Secondly I would like more research into what causes SCAD, especially in relation to hormones.
Finding common pre-symptoms/conditions which could alert medical professionals to possible early diagnosis, thus preventing heart attacks. Maybe a standard screening test for FMD for those who may be at risk & for those who were diagnosed with SCAD before the link with FMD was known.
Educating medical practitioners. They are clueless and its terrifying
why and how to prevent
Education of medical personnel.
The cause of the coronary artery tear.

Research on the medical history of patients who only have 1 SCAD compared to those who have had 2,3,4 or 5 SCADs - what is the trigger - are there different triggers for different age groups? Those who have had multiple SCADs are of a certain age? Are you more at risk the younger you are? We are of varying ages, medical histories, general fitness so medication should be determined on medical history and on the severity of the individual's SCAD. I am over 7 years post Scad so Cardiac rehab which is relevant for Scad patients would be helpful at the time but not now. I was a RN for nearly 40 years and I never heard of SCAD, so Nurse education is needed as well as on going education for Doctors, not only in hospital settings but in the general commmunity.
Cause and preventative measures for recurrence
Why does SCAD occur?? What are the risk factors and what is the likelihood of another SCAD attack occurring
All of the above A treatment so it doesn't happen again.
The cause of SCAD and risk of future occurrence. Is medication needed ongoing
What causes it, risk factors, possible early warning signs, psychological impact
Finding reasons why perfectly health women have SCAD. I was 66 but in really good health and exercised daily. I was shocked to find out I had an artery tear.
An explanation and understanding of ongoing pain/ discomfort issues would be useful, especially in the context of SCAD supposedly being healed in 5 weeks...
Working on the two questions ticked above.
Understanding risk to other family members

I would like them to focus on research to stop younger women having these issues. I worry about my daughters coming into child bearing age.
My older sister also has now had 2 SCAD H/A within the last 4 years which I have suffered 3 SCAD H/A I would like to see more with regards to the genetics as I have young daughters would be good to know more
Definitely the genetic link.
Finding the key of why it happens. Being on tablets as a preventative is not great.
Medical staff and the public are unaware of this condition. I left the hospital with a pamphlet on heart attacks but it was in no way specific to SCAD. I felt alone, confused and anxious with no information at my disposal.
What is the cause of SCAD and how to stop it happening again
Cause and treatment
All of the above. To have a second SCAD 8 weeks ago and return to ED to see they still know nothing about it. To be transferred to a cardiac hospital (private) and have nurses know nothing.
I personally think focus on all of the above. However from someone who has had a SCAD I am petrified of it happening again. It's been almost 3 years for me, and I do still think of it daily. So perhaps focusing on why this happened, and how to prevent it in the future would be a priority for me. Thank you
How to prevent future SCADS in patients who have previously had one and more education to healthcare professionals
Ongoing chest pain when heart has resolved itself

Why it happens and if it will happen again.
Understanding why/how the artery tears. Once this is established more can be done to educate and treat scad?
I'd love to know why arteries tear. And if the current clinical guidelines are producing optimum outcomes.
Why it happens so prevention is next step. I now count the years between episodes and get more anxious as it gets closer to the gap between each. Thought I was in the clear with last three being 2004 then 2009 and then 2017 so I figure any time now..
A successful treatment for SCAD
The reasons for SCAD are not clear and there are no preventions. Why does it happen? Apart from hormones, stress, extreme exertion etc, more research needs to be done to find the reason and prevent this happening in the future. Especially for young people.
Why it occurs, what is the relevance with migraine, does migraine cause scad or do triptans increase the risk by weakening arteries, is stress the cause or how people manage the stress ie increased caffeine for lack of sleep. Also, do the Az and Pfizer immunisation and/or covid infection have a link to development of scad. subsequently, understanding cause should hopefully guide appropriate treatment.
Everything, as so much is unknown. Causes, prevention, genetic link (if any), treatment and awareness. I even had a nurse that had been working in a cardiac ward for 30 years and she had not heard of it before.

Ensuring it could happen to anyone, I didn't experience the normal heart attack symptoms but I knew something was right to went to my GP not all would do this. So getting info out there to those people
Causes such as pre eclampsia, coronary microvascular disease, stress hormones, hormone replacement therapy, over exertion, untreated hypertension, FMD.
Cause and how we can prevent
lack of knowledge of SCAD by health professionals. SCAD specific patient information and rehab. Prevention strategies
Educating smaller hospitals
Proper follow up, I was discharged from Fiona Stanley Hospital after 4days with a bag of meds and to just get in touch with my GP and phone hookup planned in 10weeks, piss poor and very anxious, alone, in the dark of how to go forward
The cause and the correct treatment
Why Young fit women who suffer cardiac arrest and their recovery
Research and awareness has come a long way in 10/15yrs. My 1st SCAD went undiagnosed as I "was too young to have a heart attack ". Presented back to ED 2 months later with a blockage/heart attack. 2nd Scad, 10yrs later, when I presented to ED they knew exactly what was going on and called the Cath lab in that night for an angiogram to diagnose. Medication was a lot better too with 2nd Scad.
1. Feedback to participants. 2. Assist participant/s with stumbling blocks in obtaining parent's autopsy reports 50+ years without obtaining permission from a sibling.

Genetic risk factors Stress impact re cause of SCAD Need for statins and asprin
Would be great to understand the why scad occurs
While I was in hospital after my SCAD I was looking up various information online, and I came across the American Heart Association's 'SCAD: Current State of the Science' scientific statement. It is a detailed document that outlines the standards in the US for the treatment of SCAD, including recommended follow-up investigations, etc. I do not know if there is a similar document in Australia, but I think there needs to be one if there isn't, so that to guide doctors on how SCAD patients should be treated, including how this treatment may differ from the treatment of traditional heart attack patients. For e.g. the US statement recommends that routine Heparin administration to prevent clots should be avoided with SCAD patients as it can accentuate bleeding. I was administered Heparin whilst in hospital, and when I raised my concerns with the treating doctor, the response was that it was standard practice for all heart attack patients. The US statement also discusses screening for FMD and genetic conditions associated with SCAD. I had to push for genetic screening for myself even though my sister passed away from SCAD, and I am currently awaiting the findings. From what I have gathered from Facebook SCAD groups, there are also differing methods being recommended for FMD screening ranging from renal and carotid ultrasounds, to full body CT scans. So, I think researchers should focus on developing a document like the US document that outlines the standard treatment and minimum follow-up investigations that should be conducted in each SCAD case. But also as a mother of 3, an aunt of 2 (my sister's children) and a grandmother of 2, it is very important for me to determine if other

family members may be at risk, so I think that research into SCAD genetics is also imperative.
information on why this occurred and the likelihood of it happening again so that the dear factor can be contained somewhat causes and cure as I feel we are somewhat on our own. being told to join a Facebook group for a medical episode shouldn't be the best firm of information
Focus on training doctors to look at the big picture... not just theie area. I have a cardioligist. Neuroligist and an endocronoligist. And all they do is focus on their area... not the whole person.
Identifying people at risk and educating the public on recognising the symptoms so they get the help they need in a timely fashion. I was relaxing with a cup of tea when I had my first SCAD and asleep when I had my second one week later. Stress, fitness, family history, high blood pressure, cholesterol or poor health was not a factor. I would like to know what caused it.
Finding the connection and any precursors
understanding why the heart artery tears in the first place, determining who is most at risk and pyschological impacts and how to manage post SCAD and also drugs that don't make people so tired and fatigued
Best treatment protocol and ensuring all cardiologists are aware of this for SCAD. My cardiologist 'googled' the treatment protocol
Uncovering the underlying cause of SCAD
Whether survivors of SCAD are more likely to suffer another attack.

Improving education to all GPS and cardiologists.
Focus should be on the underlying cause of SCAD in an attempt for cardiologists GPs and health care providers to have a real understanding of the complexities of this illness particularly if FMD is the cause.
Why some people have SCAD once and others have several episodes.
What I ticked above, finding out the why, best treatments, education of medical professionals as I was diagnosed with SCAD 5 years after the fact.
Reason for SCAD occuring
Are the medications necessary? in the scad survivors group, this varies greatly. I'm still on so many and they impact on my legs and cause cellulite and issues with circulation. Very different from prescad when I was muscular and very fit. I don't do such high impact exercise anymore so that probably hasn't helped either, but my body is different. High blood pressure now if I try to go off the meds... not too high beforehand. The super high statins were terrible for my memory and legs and no one supported me re deciding to stop taking them. Cardiologist not available to discuss and GP fobbed me off. Thank you.
Medication manage and protocols and DNA research
Awareness
Understanding why it happens and how avoid having another one.
Prevention
The treatments and educating doctors. I had 3 stents and I should never have had them put in as they failed within 5 months.

Stress related to scad and public awareness. The ambulance officers who treated me had not heard of it
Finding out the causes and consequently developing prevention strategies
As above
The reasons why SCAD occurs and the best treatments for SCAD. I had another SCAD immediately after the stent was put in place, so perhaps I've had 3 episodes. Did the CABG cause further damage?
Getting the research that they do have to survivors, both those recovering in hospital and those who have left hospital, as soon as update research is available. Knowledge is power for survivors (the opposite is true too).
Obviously a good treatment should be a key goal. Education of doctors and medical staff - People with chest pain are still treated like they could be imagining it, if they don't fit the stereotypical overweight/ smoker/drinker. Genetics work is also important.
Medical Care I received was pretty awful, I was moved to another hospital for diagnosis as the hospital I was first taken to had no idea what was happening. They even tried to discharge me because they thought I was fine.
Use a big data to predict future and to analyze the back ground/cause
Looking at the blood pressure/heart rate , with physical exercise and stress levels (although difficult to record) of people who have experienced a SCAD that do NOT have any underlying genetic disorders (ie. FMD) to try and determine a common factor.

There needs to be a specific SCAD treatment plan given to patients immediately. The lack of knowledge amongst GPs, Cardiologists and Cardiac Rehab is extremely worrying and dangerous. Patients are in so much shock and have a lot of uncertainty to deal with being diagnosed with SCAD and they shouldn't have to educate themselves and their medical professionals on their condition and best practice treatment. SCAD patients need to stop being treated like "typical" heart attack patients as it adds to the SCAD patients anxiety and concerns as to whether they are actually on the right medication and getting the best advice. I had to change Cardiologists 3 times before it was discovered that my SCAD had not healed and I needed an urgent stent placed. I was glad I trusted my instincts and didn't listen to the medical professionals telling me everything was ok. I was put through 4 stress tests and told I was all good and just stay on medication for life. This was not ok with me and I kept asking for a CTCA to physically prove that the SCAD had healed. Thankfully Prof Bob Graham agreed to see me and review my case and medication and discovered that my LAD was completely blocked and needed an urgent intervention. This should have been discovered much earlier than 14 months after SCAD. A CTCA should be a mandatory test 3-4 months after SCAD to ensure everything has healed if the SCAD has been medically treated. Cardiac Rehab should be recommended to all SCAD patients and they should be given a treatment plan to give to their rehab. My hospital discharge patients from Monash Heart said "cardiac rehab" not required!
Understanding and therefore preventing post SCAD chest pain
Think awareness to doctors and nurses. And public. It can happen to anyone, anywhere Or can it? I guess finding out why? And if my sons may get it. I just

wish when it happened I and my dr had more knowledge. After they didn't book me in to see him for 1yr check up. In that year I felt scared abd alone and had ptsd. More support after would have been helpful. He took me off meds on that 1yr apt. And I said what happens if I have another one. Abd he said go to the hospital like anyone would. That was it. Then 1yr later another check up with dif cardiologistwho kind of new nothing. Nothing. Then 3rd year check up with same 2nd dr who said why aren't you on medication. 3yrs later 😳 so I've just been prescribed 3 new drugs after 3 yrs off anything. Thats scary and makes me feel I slipped through the cracks. More knowledge, more support for aftercare in first few years.
Anxiety is driven by not knowing the 'why' for me so that would be a major focus. I have been diagnosed with FMD but not in my heart. I want to know why and if there are family or genetic links.
Treatments post scad, and better medications
As above
Post SCAD psychological support , and the importance of it, as even though I feel well, at the back of my mind I wonder if it will happen again. I have had 2x episodes of indigestion, and wait for the pain to godown my arm. 😟
Treatment and ongoing monitoring
Why does it occur?
It seems understanding is in its infancy, as such a holistic understanding is required.
Education of health professionals and public. Need for SCAD specific rehabilitation and mental health support (it is a traumatic event).

Please please do something about the recognition of symptoms of scad in otherwise healthy young women. I nearly died because it wasn't recognised and I ended up with much more damage due to a total RCA dissection after original hospital stented arteries and told me it must be heart disease (after telling me it couldn't be heart related because I didn't have typical symptoms). I felt like they thought I was making up the shoulder blade pain! The next week I had 3 ambulances rush me to a different hospital because of total spiral dissection that could have been avoided if I had received recommended conservative treatment. My symptoms and presentation were cookie cutter SCAD. I am AMAZED that it wasn't recognised, now that I know the disease and the background. I am so fed up seeing tv news talk about heart attack risks and latest research and yet they neglect to warn the public and medical professionals about SCAD and how it presents. It has changed my life and I have very little energy at times and have gained weight and feel so much older and tired. I so wish it had been recognised and treated correctly. I now have 7 stents and wiring in my RCA and a pretty traumatic coronary angiogram story x2. Thankyou.
The preventive measures
Educating medical staff. Although I had a good experience there are many who were not diagnosed early. Underlying reasons in those without FMD
I think researchers should focus on early diagnosis of potential SCADsters and education so SCADs become very rare but are treated seriously and understood by staff and patients.
understanding underlying reason in fit healthy people often young but in my case 55

all of the above. and the affect pregnancy and IVF has on increasing chances of a SCAD in someone who mine be predisposed. Also because there are a lot of young women that are told not to get pregnant post SCAD. More research on the repercussions of pregnancy and risk is important for quality of family life and decisions they may undertake when trying to decide to whether have children
All the above. All are vitally important to the diagnosis, treatment and general public awareness of this health issue.
EDUCATION and TREATMENT "Education" of all medical staff. The contrast between the treatment and SCAD knowledge of my two SCAD episodes is incredible. It's getting better but it is luck to happen upon knowledgeable staff and not across the board. "Treatment" is so varied and Cardiologists disagree often on best practice.
I believe in prevention rather than cure so it would be great if we could work why this occurs and learn how to stop it in it's tracks.
I think awareness levels are hugely improved fir hospitals. priority now is how to prevent by understanding the cause
Everything mentioned above is so important. I went from never hearing about SCAD to one day feeling unwell and ending up in emergency having had a heart attack with no obvious risk factors. It was so scary not knowing what was happening and to top it off the cardiologist in the hospital could not give me much information, he told me to 'google it' (hence why I went on a search for Professor Robert Graham). Your world changes when suddenly you are on medication for the rest of your life and you don't know why. I think all areas mentioned above are important for the

patients health and mental wellbeing as well as raising awareness so others who may be at risk know about it.
More awareness to the general public. Including myself I was completely unaware of SCAD till late June this year. Even having a heart attack was not what I thought would happen so doubted that I was having one. More focus on how heart attacks present. I know we hear alot about heart attacks but in rehabilitation I have learnt that even one is different.
Impacts of COVID-19 on SCAD recovery.
What are the causes of scad.
education
To understabd why it happened, screening and ultimately prevention
Why do so many SCAD survivors have post SCAD pain for so long?
How to ultimately avoid it.
Focus on what helps the scad victim ie how long does it take to heal, what medication really helps, educating specialists on scad. Some doctors and specialists I feel don't know enough about scad or how to treat it, nor do they listen or give you explanations or options when you try to explain the different symptoms you are experiencing, maybe this is due to them not understanding or knowing what to do.
I'd like more information on the data of reoccurrence. It's a big anxiety for SCAD people and it's about 30%. I'd like more research on the reoccurring people.

I know the main after effects for me after my SCAD is the medication effects especially the beta blockers. I have also been limited with ability to lift which has made my arms and shoulders weak. The after SCAD life effects is something I would like researched
I think what causes it, find that and then hopefully, it can be prevented!!
Being on medication for the rest of my life causes me great anxiety, fear and concern so as above, research into the best medical treatments for SCAD and the duration of same if not for life.
research to gain an understanding into why SCAD occurs
Underlying cause and improved medical education to the medical profession
What patients are more likely to have another scad and why?
Cause
Awareness, likelihood of reoccurrence
The whole cycle in order (1) why they happen; (2) increasing awareness to enable detection and treatment, (3) medical treatments and then (4) managing SCAD. My situation was slightly different due to my existing heart conditions and subsequent issues. Compared to my other heart treatments, SCAD was difficult in terms of diagnosis, treatment and rehabilitation. I was very lucky in that an incredibly knowledgeable cardiologist first treated me, my old GP had experience with SCAD and due to COVID could do telehealth (my new GP knew nothing about SCAD) and I was able to tap into the international community of SCAD survivors. One other issue - insurance. I have not been able to return to my role at work. One insurance company has treated me with great respect and understanding and worked through

SCAD and its uniqueness with me. The other insurance company has been hopeless and have not even tried to understand the diagnosis in the context of their policy framework.
Treatment and prognosis, likelihood of repeat occurrence, genetic testing. Cause?
All of them. I have been shocked how relatively common it is, yet no one I know has ever heard of it, so awareness is key, especially as women's symptoms seem to be less dramatic than men's - or they tolerate pain better and soldier on... I absolutely want to know WHY it happens - I have zero risk factors for heart attack, am fit and healthy and exercise every day. But I guess most important is discovering the best medical treatments for those who suffer it, especially as most seem to be very healthy, and can't modify diet etc to help heal, as it's already good.
How best to train medical staff to recognise symptoms and how to treat the condition
What is the best treatment frequent checks behire scad happens again

Chapter 8: paper 6 supplementary materials

Supplementary table 1 – Frequency of each EQ-5D health status

EQ-5D status	Frequency	Percentage
11111	47	24.4
11112	35	18.1
11222	23	11.9
11122	12	6.2
11212	12	6.2
11221	11	5.7
21222	9	4.7
11211	6	3.1
11121	4	2.1
21221	4	2.1
11223	3	1.6
11311	2	1
11312	2	1
11321	2	1
21211	2	1
21223	2	1
21321	2	1

22222	2	1
11113	1	0.5
11213	1	0.5
11322	1	0.5
21111	1	0.5
21122	1	0.5
21132	1	0.5
21232	1	0.5
21311	1	0.5
21322	1	0.5
22321	1	0.5
22322	1	0.5
22333	1	0.5
33323	1	0.5

Supplementary table 2 – Comparison between people who completed and who did not complete the EQ-5D questionnaire

Characteristics	Responders	Non-responders	P value
Age at SCAD diagnosis, mean±SD (years)	52.7±10.7	53.6±11.6	0.69
Female sex	172 (89.1%)	23 (69.7%)	0.002 *
Body Mass Index, mean±SD (kg/m^2)	28.2±6.2	26.6±77	0.28
Caucasian	159 (82.4%)	25 (62.5%)	0.005 *
Current or ex-smoker	59 (30.7%)	14 (46%)	0.08
Type of ACS • ST elevation myocardial infarction • Non-ST elevation ACS	 65 (33.7%) 128 (66.3%)	 10 (25%) 20 (75%)	 0.29 0.29
Percutaneous coronary intervention performed	22 (11.4%)	1 (2.5%)	0.14
LVEF assessed - Of those assessed, LVEF≤40%	171 (88.6%) 15 (8.8%)	29 (72.5%) 2 (6.9%)	0.008 * 1.0

ACS: acute coronary syndrome, LVEF: left ventricular ejection fraction, SCAD: spontaneous coronary artery dissection,