frontiers | Research Topics

Spontaneous coronary artery dissection: Current state of diagnosis and treatment

Edited by
Svetlana Radomir Apostolović, Srdjan Aleksandric, Branko Dusan Beleslin and Jacek Bil

Published in
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-8325-5214-8
DOI 10.3389/978-2-8325-5214-8

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Spontaneous coronary artery dissection: Current state of diagnosis and treatment

Topic editors

Svetlana Radomir Apostolović — University Clinical center, Serbia

Srdjan Aleksandric — University of Belgrade, Serbia

Branko Dusan Beleslin — Institute for Cardiovascular Diseases, Clinical Center of Serbia, Serbia

Jacek Bil — Medical Centre for Postgraduate Education, Poland

Citation

Apostolović, S. R., Aleksandric, S., Beleslin, B. D., Bil, J., eds. (2024). *Spontaneous coronary artery dissection: Current state of diagnosis and treatment*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5214-8

Table of contents

frontiers | Frontiers in Cardiovascular Medicine

TYPE Editorial
PUBLISHED 12 July 2024
DOI 10.3389/fcvm.2024.1455983

OPEN ACCESS

EDITED AND REVIEWED BY
Tommaso Gori,
Johannes Gutenberg University Mainz, Germany

*CORRESPONDENCE
Srdjan Aleksandric
srdjanaleksandric@gmail.com

RECEIVED 27 June 2024
ACCEPTED 28 June 2024
PUBLISHED 12 July 2024

CITATION
Apostolovic S, Aleksandric S and Beleslin B (2024) Editorial: Spontaneous coronary artery dissection: current state of diagnosis and treatment.
Front. Cardiovasc. Med. 11:1455983.
doi: 10.3389/fcvm.2024.1455983

Editorial: Spontaneous coronary artery dissection: current state of diagnosis and treatment

Svetlana Apostolovic[1,2], Srdjan Aleksandric[3,4]* and Branko Beleslin[3,4]

[1]Cardiology Clinic, University Clinical Center of Nis, Nis, Serbia, [2]Medical Faculty, University of Nis, Nis, Serbia, [3]Cardiology Clinic, University Clinical Center of Serbia, Belgrade, Serbia, [4]Faculty of Medicine, University of Belgrade, Belgrade, Serbia

KEYWORDS

spontaneous coronary artery dissection (SCAD), acute coronary syndrome (ACS), intravascular imaging, intravascular ultrasound (IVUS), optical coherence tomography (OCT), percutaneous coronary intervention (PCI), cutting balloon (CB)

Editorial on the Research Topic
Spontaneous coronary artery dissection: current state of diagnosis and treatment

Spontaneous coronary artery dissection (SCAD) is relatively rare but potentially life-threatening condition characterized by the spontaneous separation of the layers of the coronary artery wall and the formation of intramural hematoma which compromises coronary blood flow (1, 2). Djokovic et al. discussed several mechanisms and theories to understand development of SCAD, including primarily structural weaknesses in the arterial wall with abnormalities in the connective tissue or smooth muscle cells predisposing spontaneous tearing or separation ("inside-out" or "outside in" hypothesis) (1, 2). Ultimately, the pathophysiology of SCAD likely involves a complex interplay of structural, hormonal, inflammatory, and genetic factors, highlighting the need for comprehensive research (3). Stanojević et al. discussed the most common predisposing factor like fibromuscular dysplasia, followed by inherited connective tissue disorders and systemic inflammatory diseases. Pregnancy and the use of sex hormones are common in younger females with SCAD. It was found that around 43% of acute coronary syndromes (ACS) cases among pregnant or postpartum women were caused by SCAD. It is also important to note that the presence of traditional risk factors for atherosclerosis does not exclude SCAD as a diagnosis in young patients with ACS.

Invasive coronary angiography remains the most important diagnostic tool in suspected SCAD, and Kovacevic et al. discussed the angiographic presentation of SCAD. According to Yip-Saw classification (4), there are three typical angiographic patterns of SCAD, but several potential pitfalls and essential differential diagnoses should be considered. Type 1 SCAD is characterized by a pathognomonic angiographic appearance and a recognizable radiolucent flap, usually affecting the proximal segments of coronary arteries. Type 2 SCAD is the most common type, presents as a smooth diffuse stenosis either with lumen restoration in the distal segment (Type 2a) or stenosis extending till the end of the artery (Type 2b). In addition to atherosclerosis, the most common mimic of SCAD type 2 is coronary vasospasm (focal or diffuse), which can be distinguished with intracoronary nitroglycerine injections. Type 3 SCAD

is characterized by focal stenosis and underlying hematoma resembling a ruptured atherosclerotic plaque and is frequently missed by coronary angiography alone. Therefore, to distinguish features that mimic SCAD, high-resolution intracoronary imaging techniques such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), may be beneficial. Recently, additional type 4 SCAD has been proposed to describe total vessel occlusion, usually of a distal coronary artery (5). It is particularly challenging to diagnose, and is often misinterpreted as an atherosclerotic occlusion, thus being treated systematically by percutaneous coronary intervention (PCI). As type 4 SCAD often coexists with other SCAD types or occurs as a consequence of their progression, an intramural hematoma near the occlusion could be identified with intravascular imaging techniques. Krljanac et al. described the role of multimodality imaging, especially echocardiography and cardiac magnetic imaging (CMR), in the evaluation and follow-up of SCAD patients presenting with ST-elevation myocardial infarction (STEMI) (6). Previous studies showed that the majority of these patients have a mild myocardial infarctions and preserved or slightly impaired left ventricle (LV) systolic function (7). Therefore, the improvement in LV systolic function during follow-up is greater than that seen in patients with type 1 STEMI. These differences may be related to a higher prevalence of TIMI 3 flow at coronary angiography and an overall smaller ischemic burden in STEMI patients caused by SCAD than in those caused by erosion/rupture of the atherosclerotic plaque and subsequent thrombosis. However, there is no assurance that this applies to more complex types of SCAD, such as total vessel occlusion and multisegmental or multivessel engagement.

Mehmedbegovic et al. pointed out the importance of intravascular imaging techniques (IVUS and OCT) in the differential diagnosis between SCAD and other coronary lesions such as atherosclerotic plaque with or without intracoronary thrombus or myocardial bridging. The main disadvantage of invasive coronary angiography is that it is basically just a "luminography" that provides little information regarding artery wall integrity. Quite the opposite, IVUS and OCT would provide detailed phenomena typical of SCAD-like lesions such as the existence of an intimal flap, the presence and extent of intramural hematoma and/or thrombus, and the absence of atherosclerotic changes in the arterial wall. Intravascular imaging should therefore only be used if angiographic findings are unclear in large arteries (especially in SCAD types 3 and 4) and/or if further PCI is required (8–11). Current treatment strategies for SCAD patients were explained in detail in a comprehensive review by Ilic et al. (Figure 1). While no randomized clinical trials have been conducted on medical treatment for SCAD, treatment strategies generally emphasize a conservative approach since spontaneous healing of SCAD usually occurs in the first 30 days after the event (12, 13). Percutaneous coronary intervention is recommended for patients with ongoing ischemia and/or hemodynamic instability due to its high complication rates and low angiographic success rates (12, 14). However, the multicentre international "DIssezioni Spontanee COronariche (DISCO)" registry, which included 314 SCAD-patients, found that dual

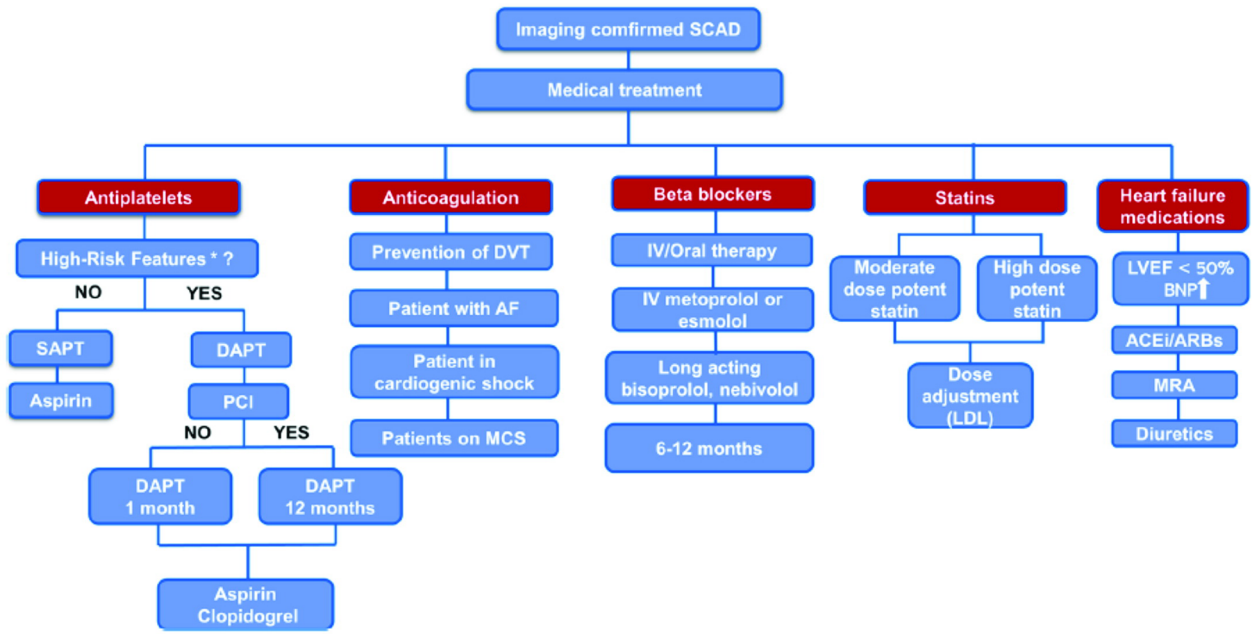


FIGURE 1
Proposed algorithm for medical treatment of imaging confirmed SCAD. *"high-risk" features - concomitant atherosclerosis, large thrombus burden, critical stenosis that was left untreated, and significant flow impairment in the affected coronary artery. AF, atrial fibrillation; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BNP, brain natriuretic peptide; DAPT, dual antiplatelet therapy; DVT, deep vein thrombosis; IV, intravenous; LVEF, left ventricle ejection fraction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

antiplatelet therapy (DAPT) was associated with a 2.6-fold higher risk for major adverse cardiovascular events (MACE) compared to single antiplatelet therapy (SAPT) with mainly aspirin at 1-year follow-up (15). These findings implicate that DAPT could be harmful in conservatively managed SCAD patients, especially those with intramural haematoma due to intramural bleeding aggravation, haematoma and dissection propagation and subsequent arterial lumen compression (15). Therefore, there is consensus that DAPT should be prescribed in SCAD patients, consisting of aspirin and clopidogrel, and should be limited to the first 30 days following hospital admission, except for those with stent implantation who should be treated in accordance with the current guidelines for ACS (1, 14). It is recommended to continue taking aspirin monotherapy after 1 month, but the duration of this therapy remains unknown. The current recommendations also support the use of beta-blockers as a first-line therapy for at least 1 year after the event since their use was associated with a significantly lower risk of SCAD recurrence (16). Other medications such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), mineralocorticoid antagonists, loop diuretics and statins are recommended for patients with concomitant risk factors for atherosclerosis and coronary artery disease and/or heart failure with reduced or mild ejection fraction (EF<50%), in accordance with the current guidelines.

A percutaneous angioplasty using a cutting balloon as a novel interventional strategy for the treatment of SCAD was described by Maricic et al. This technique entails positioning of a cutting balloon inside the true lumen to cause controlled micro-incisions within the affected vessel, causing intimal fenestration and hematoma draining (1, 17). Consequently, the true arterial lumen is decompressed, and coronary blood flow is restored. According to current data, by using a smaller cutting balloon than the reference vessel diameter, the risk of vessel injury can be minimized, and the procedure can be more effective. The most often procedure complication is distal propagation of the subintimal hematoma with dissection extension, while coronary perforation and acute vessel closure are very rare. If such a situation arises, stenting may be the only option to stabilize the dissected coronary artery and provide additional support. Further research is needed to determine the long-term clinical implications and compare the efficacy and safety of cutting balloon angioplasty with other treatment options for SCAD.

A systematic review by Petrovic et al., which included 13 observational studies, examined clinical outcomes in 1,801 patients with SCAD treated conservatively (65%) or invasively (PCI 33%; coronary artery bypass grafting 1.3%). Percutaneous coronary intervention was associated with a higher rate of periprocedural complications, mostly hematoma extension and/or iatrogenic dissection, which frequently required the implantation of at least three stents with residual areas of dissection. The overall reported in-hospital and follow-up mortality rates were 1.2% and 1.3%, respectively. According to these results, conservative treatment is the preferred treatment option for patients with SCAD. A review by Apostolovic et al. focused on female patients in generative period (16–55 of age) with ACS caused by SCAD and compared clinical characteristics and outcomes between non-pregnant women with SCAD and pregnant women with SCAD. Compared to non-pregnant women, pregnant women have a greater chance of having SCAD in the left main and/or the left anterior descending artery (LAD); are more likely to have STEMI; and are more likely to undergo PCI. However, there were no differences regarding mortality rates or recurrent coronary dissection between these two study groups. Future research efforts with developing specialized SCAD registries will contribute to a better understanding of this condition and its outcomes.

Author contributions

SAp: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. SAl: Writing – review & editing, Writing – original draft, Validation, Conceptualization. BB: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Adlam D, Alfonso F, Maas A, Vrints C Writing Committee. European Society of cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J.* (2018) 39(36):3353–68. doi: 10.1093/eurheartj/ehy080

2. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. American Heart Association Council on peripheral vascular disease; council on clinical cardiology; council on cardiovascular and stroke nursing; council on genomic and precision medicine; and stroke council. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation*. (2018) 137(19):e523–57. doi: 10.1161/CIR.0000000000000564

3. Adlam D, Berrandou TE, Georges A, Nelson CP, Giannoulatou E, Henry J, et al. Genome-wide association meta-analysis of spontaneous coronary artery dissection identifies risk variants and genes related to artery integrity and tissue-mediated coagulation. *Nat Genet*. (2023) 55(6):964–72. doi: 10.1038/s41588-023-01410-1

4. Yip A, Saw J. Spontaneous coronary artery dissection-A review. *Cardiovasc Diagn Ther*. (2015) 5(1):37–48. doi: 10.3978/j.issn.2223-3652.2015.01.08

5. Al-Hussaini A, Adlam D. Spontaneous coronary artery dissection. *Heart Br Card Soc*. (2017) 103(13):1043–51. doi: 10.1136/heartjnl-2016-310320

6. Krljanac G, Apostolovic S, Polovina M, Maksimovic R, Nedeljkovic Arsenovic O, Djordjevic N, et al. The follow-up of myocardial injury and left ventricular function after spontaneous coronary artery dissection. *Front Cardiovasc Med*. (2023) 10:1276347. doi: 10.3389/fcvm.2023.1276347

7. Díez-Villanueva P, García-Guimarães M, Sanz-Ruiz R, Sabaté M, Macaya F, Roura G, et al. Prognostic implications of left ventricular systolic dysfunction in patients with spontaneous coronary artery dissection. *Eur Heart J*. (2023) 12:299–305. doi: 10.1093/ehjacc/zuad035

8. Gudenkauf B, Hays AG, Tamis-Holland J, Trost J, Ambinder DI, Wu KC, et al. Role of multimodality imaging in the assessment of myocardial infarction with nonobstructive coronary arteries: beyond conventional coronary angiography. *J Am Heart Assoc*. (2022) 11(1):e022787. doi: 10.1161/JAHA.121.022787

9. Johnson TW, Räber L, di Mario C, Bourantas C, Jia H, Mattesini A, et al. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European association of percutaneous cardiovascular interventions. *Eur Heart J*. (2019) 40(31):2566–84. doi: 10.1093/eurheartj/ehz332

10. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European association of percutaneous cardiovascular interventions. *Eur Heart J*. (2018) 39(35):3281–300. doi: 10.1093/eurheartj/ehy285

11. Prakash R, Starovoytov A, Heydari M, Mancini GB, Saw J. Catheter-induced iatrogenic coronary artery dissection in patients with spontaneous coronary artery dissection. *JACC Cardiovasc Interv*. (2016) 9(17):1851–3. doi: 10.1016/j.jcin.2016.06.026

12. Bocchino PP, Angelini F, Franchin L, D'Ascenzo F, Fortuni F, De Filippo O, et al. Invasive versus conservative management in spontaneous coronary artery dissection: a meta-analysis and meta-regression study. *Hellenic J Cardiol*. (2021) 62 (4):297–303. doi: 10.1016/j.hjc.2021.02.013

13. Hassan S, Prakash R, Starovoytov A, Saw J. Natural history of spontaneous coronary artery dissection with spontaneous angiographic healing. *JACC Cardiovasc Interv*. (2019) 12(6):518–27. doi: 10.1016/j.jcin.2018.12.011

14. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Dan GA, et al. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J*. (2023) 44 (38):3720–826. doi: 10.1093/eurheartj/ehad191

15. Cerrato E, Giacobbe F, Quadri G, Macaya F, Bianco M, Mori R, et al. Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry. *Eur Heart J*. (2021) 42 (33):3161–71. doi: 10.1093/eurheartj/ehab372

16. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol*. (2017) 70(9):1148–58. doi: 10.1016/j.jacc.2017.06.053

17. Alfonso F, Paulo M, Lennie V, Dutary J, Bernardo E, Jiménez-Quevedo P, et al. Spontaneous coronary artery dissection: long-term follow-up of a large series of patients prospectively managed with a "conservative" therapeutic strategy. *JACC Cardiovasc Interv*. (2012) 5(10):1062–70. doi: 10.1016/j.jcin.2012.06.014

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 18 October 2023
DOI 10.3389/fcvm.2023.1270259

OPEN ACCESS

EDITED BY
Konstantinos Koskinas,
Inselspital University Hospital Bern, Switzerland

REVIEWED BY
Vincent Roule,
Centre Hospitalier Universitaire de Caen, France
Jonas Häner,
University Hospital of Bern, Switzerland

*CORRESPONDENCE
Zlatko Mehmedbegović
✉ zlatkombegovic@gmail.com

RECEIVED 31 July 2023
ACCEPTED 18 September 2023
PUBLISHED 18 October 2023

CITATION
Mehmedbegović Z, Ivanov I, Čanković M, Perišić Z, Kostić T, Maričić B, Krljanac G, Beleslin B and Apostolović S (2023) Invasive imaging modalities in a spontaneous coronary artery dissection: when "believing is seeing". Front. Cardiovasc. Med. 10:1270259. doi: 10.3389/fcvm.2023.1270259

Invasive imaging modalities in a spontaneous coronary artery dissection: when "believing is seeing"

Zlatko Mehmedbegović[1,2]*, Igor Ivanov[3,4], Milenko Čanković[3,4], Zoran Perišić[5,6], Tomislav Kostić[5,6], Bojan Maričić[6], Gordana Krljanac[1,2], Branko Beleslin[1,2] and Svetlana Apostolović[5,6]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Serbia, [2]Department of Cardiology, University Clinical Center of Serbia, Belgrade, Serbia, [3]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia, [4]Cardiology Clinic, Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia, [5]Faculty of Medicine, University of Niš, Niš, Serbia, [6]Division of Interventional Cardiology, University Clinical Center Niš, Niš, Serbia

Spontaneous coronary artery dissection (SCAD) is a rare but increasingly recognized cause of acute coronary syndrome (ACS) with recent advancements in cardiac imaging facilitating its identification. However, SCAD is still often misdiagnosed due to the absence of angiographic hallmarks in a significant number of cases, highlighting the importance of meticulous interpretation of angiographic findings and, when necessary, additional usage of intravascular imaging to verify changes in arterial wall integrity and identify specific pathoanatomical features associated with SCAD. Accurate diagnosis of SCAD is crucial, as the optimal management strategies for patients with SCAD differ from those with atherosclerotic coronary disease. Current treatment strategies favor a conservative approach, wherein intervention is reserved for cases with persistent ischemia, patients with high-risk coronary anatomy, or patients with hemodynamic instability. In this paper, we provide a preview of invasive imaging modalities and classical angiographic and intravascular imaging hallmarks that may facilitate proper SCAD diagnosis.

KEYWORDS

SCAD, diagnostic algorithm, intravascular imaging, IVUS, OCT

Introduction

Spontaneous coronary arterial dissection (SCAD) is widely recognized as one of the causes of acute coronary syndrome (ACS) (1, 2). SCAD starts with the initial formation of a hematoma in the tunica media within the coronary vessel wall (inside-out mechanism) (3). Intramural hematoma may progress distally and circumferentially along the vessel wall compressing the true lumen, resulting in flow disturbances or even complete artery blockage (**Figures 2A,C**). Hematoma as the initial damage to the vessel wall integrity can subsequently lead to an intimal tear, which gives SCAD its classic angiographic recognition—such as lumen compression, dissection stripes, or a combination of both, and even complete occlusion in some cases (**Figures 2B,D**). Irrespective of the underlying substrate, the resulting compression of the true lumen clinically produces classical symptoms of ACS. However, the diagnosis of SCAD among patients with ACS might be challenging when relying exclusively on clinical presentation (4). Differential diagnosis of SCAD from common atherothrombotic ACS events is

difficult due to the overlapping findings obtained from non-invasive diagnostic modalities such as cardio-specific biomarkers and electrocardiographic or echocardiographic examinations (5). Contemporary non-invasive diagnostic modality for coronary artery visualization, such as multislice computed tomography coronary angiography (MSCT-CA), has several disadvantages, including the fact that it is not commonly employed for streamlining of ACS cases and has a lower spatial resolution, which poses challenges in accurately identifying the pathognomonic features that are crucial for SCAD diagnosis (6). Hence, the diagnosis of SCAD is still mainly based on accurately identifying and interpreting SCAD hallmarks found on invasive coronarography combined and backed-up with pretest probability of a given case (4). Despite the growing appreciation of SCAD angiographic features, the absence of specific hallmarks or angiographic similarities to other possible pathoanatomic substrates (embolus, contrast streaming, myocardial bridging, etc.) leaves significant number of SCAD cases undiagnosed, or in a later scenario, misdiagnosed (7). Therefore, in angiographically ambiguous cases, invasive intravascular modalities can provide valuable information facilitating accurate diagnosis, thereby informing further conservative treatment options or, if needed, guiding to revascularization approach (8). Further to this, SCAD patients, contrary to classic atherothrombotic events caused myocardial infarctions, are managed essentially differently, both in the Cath lab and in the coronary care intensive units (9). PCI in SCAD patients has high complication rates and low angiographic success rates, while the conservative management in majority of cases results in favorable patient outcomes with spontaneous resolution of vessel integrity (1). Thereby, for the same ACS clinical settings, physicians may choose a more conservative approach rather than an intervention-focused treatment approach for SCAD patients during regular primary PCI. In concordance with this, current consensus is that the conservative strategy is a default approach for SCAD cases, whenever it can yield positive outcomes (10). Therefore, optimal SCAD treatment relies on accurate diagnosis, commencing with high level of suspicion combined with unequivocal recognition of traditional SCAD hallmarks by invasive imaging. In this review, we will examine the diagnostic clinical work-up for SCAD, acknowledging the practical aspects of commonly used imaging modalities.

Pretest probability

The likelihood of SCAD occurring prior to a patient undergoing cardiac catheterization depends on several factors that warrant special attention in a particular case: gender, age, genetic background, clinical presentation, presence of triggering factors, hormonal changes, etc. (11). In most cases of SCAD, patients typically manifest as ACS (1). Most often, biomarkers of myocardial injury are elevated, except perhaps when the presentation is very early, as in ACS (12). Hence, diagnostic doubt should be raised in non-acute cases, but still confirmed among ACS patients. According to registries, SCAD shows gender prevalence for women (13). SCAD in males only occurs approximately 10% of the cases. SCAD accounts for more than one-third of the cases in women under 50 years of age, and up to two-thirds of all pregnancy-associated ACS. Therefore, the index of suspicion of potential SCAD should always be raised in cases involving younger female patients.

According to registries, 90% of SCAD cases have been reported to occur in patients aged 47–53 years (mean 52 years) (14). SCAD is rare in very young (less than 20 years) and very old (above 80 years) adults. Therefore, individuals presenting with symptoms outside this age range should be evaluated more carefully prior to confirming the diagnosis of SCAD; however, diagnostic alertness should not be neglected for older population.

Compared with age and gender, the presence or absence of atherosclerotic risk factors is less useful in predicting the likelihood of SCAD. Although diabetes, hyperlipidemia, and classical risk factors are rarely prediagnosed, the preexisting atherosclerotic disease burden does not exclude the SCAD diagnosis (1, 12). Specifically, hypertension can be present in approximately one-third of the patients with SCAD.

SCAD is associated with a small number of known genetic disorders. Over the past years, significant progress has been made in our understanding of the genetic causes of SCAD. Rare genetic variations, typically in genes linked to hereditary arteriopathies or connective tissue diseases [adult polycystic kidney disease, migraine, fibromuscular dysplasia (FMD), and cervical arterial dissection], are found to be associated with SCAD in up to 50% of the cases (15–17). Recent genetic research suggests that both common and uncommon genetic variables may contribute to the susceptibility to SCAD. Until further evidence, a possible diagnosis of SCAD should be considered in an ACS patient with a family history or clinical features linked to genetic disorders.

The symptoms of SCAD *per se* do not serve as reliable diagnostic differentiators, as they exhibit similarities to symptoms observed in other types of ACS (13). Certain cases have documented potentially provoking stimuli such as emotional or physical stressors. For example, in a particular scenario, if symptoms appear during or after intense isometric training, the likelihood of SCAD diagnosis increases (18). On the other hand, exposure triggers can occur along with other causes of ACS, such as Takotsubo syndrome or during vigorous activity with atherosclerotic plaque rupture. Therefore, patient behavioral factors cannot either confirm or disprove a diagnosis of SCAD but can help the physician fine-tune the level of suspicion of this entity prior to and following the findings of invasive diagnostic tests.

SCAD during pregnancy can pose a significant risk, exposing approximately 1.8% of every 100,000 pregnant women at risk in the United States (19). Available evidence suggests that pregnancy-related physiological changes present risk factors for SCAD such as high progesterone levels and the rapid changes in hormones at birth and during the postpartum period (19, 20). Hormonal background with other stressors and arteriopathies can contribute to the emergence of SCAD, alongside psychological and physical precipitating stressors that have been

identified as provoking risk factors. Similar to SCAD, fibromuscular dysplasia affects younger women and is also presently underdiagnosed (16). Because FMD affects the artery walls causing them to lose flexibility and become weak, its greater occurrence in women relative to men implicates estrogen effect, along with the evidence of other hormonal exposures such as fertility treatments, chemical contraception, hormone replacement therapy, and pregnancy, in its emergence (20). Currently, it is not fully understood if these conditions are underlying causes or occur simultaneously with SCAD.

Angiographic SCAD diagnosis

Currently, coronary angiography (CA) is the primary diagnostic modality for SCAD due to its universal availability (2). If a coronary dissection is suspected, CA should be performed as soon as possible, also in accordance with ACS treatment standards. A reliable diagnosis is crucial because the treatment for these patients differs significantly from that for ACS caused by atherosclerosis. One disadvantage is that it is essentially just a "lumenography" and provides little information regarding the integrity of the artery wall. The extreme coronary (screw-like) tortuosity, preference for the mid-to-distal segments of the vessels, absence of coexisting atherosclerosis, uniform reduction of vessel lumen, strip-like radiolucent filling defects or staining of contrast medium within the arterial wall are pathognomonic angiographic features that may indicate SCAD (21, 22). However, it should be particularly emphasized that because of the SCAD and underlying artery fragility, invasive procedure such as coronarography increases the risk of iatrogenic dissection (approximately 2%–3% risk of iatrogenic dissection is reported vs. 0.2% risk in atherosclerotic patients) (1, 23). Procedure-related dissection in SCAD patients is reported to occur in 14% of patients undergoing PCI. The commonly used classification system is proposed by Saw et al. (21), which includes three distinctive angiographic types (**Table 1**). The practicality of the proposed classification lies in the ability to suggest further imaging modality to confirm or disprove diagnosis and to indicate treatment, based on SCAD angiographic subtype.

The underlying disruption of the artery wall mainly or solely consists of intimal tear, spreading longitudinally and/or circumferentially representing anatomical substrate of SCAD type 1. Because intimal tear allows the contrast dye to enter through two flow channels, type 1 SCAD has the pathognomonic angiographic appearance of an arterial dissection, including multiple radiolucent lumens divided by radiolucent flap (**Figure 1B**).

In addition to the visible flap and the compartmentalization of the lumen, using of contrast material may result in slow clearance, hung-up, and persistent staining, with or without accompanying flow disturbance. If needed, disrupted intima can be easily visualized with optical coherence tomography (OCT), but the risk of dissection propagation during wire and catheter manipulation, as well as vigorous dye injection, must be thoroughly assessed to evaluate the expected advantages of achieving an unequivocal diagnosis.

SCAD type 2 is the most prevalent type, occurring in approximately 70% of cases. The characteristic angiographic appearance often exhibits a smooth, uniform, tubular structure with a sudden reduction in the lumen diameter (**Figures 2A,C**). The underlying substrate is compression of the true lumen by an intramural hematoma that develops suddenly and propagates distally along the vessel wall, exerting an extrinsic pressurized effect on the true lumen while leaving the intimal border intact. Type IIa lesions affect the short, localized segment of the vessel,

TABLE 1 Angiographic features of SCAD types with intravascular imaging recommendations.

SCAD	Specific diagnosis suggestive angiographic features	Intravascular imaging
Type 1	– Present in about 10%–15% cases – Pathognomonic multiple radiolucent lumen – Contrast dye staining of arterial wall – Presence or absence of dye hang-up or slow contrast clearing from the lumen – Sluggish flow at the within and after dissection segment – Requires intravascular imaging to safely guide treatment	– If needed, may be used to confirm diagnosis and to guide intervention (true lumen wire placement) and optimize result (ensure compression of false lumen) – OCT preferred due to ease of identification of intimal flap (IVUS for experienced imagers) – If used, careful manipulation is needed, since device placement can aggravate the dissection and worsen flow
Type 2	– Most prevalent (60%–75% of the patients) – Typically diffuse >20–30 mm (frequently up to most distal artery segments) – Smooth uniform narrowing (usually moderate in severity) appearing suddenly – Can mimic spasm (not responsive to nitroglycerine) – Usually, no other signs of atherosclerotic involvement	– If needed, may be used to visualize intramural hematoma volume, distribution and longitudinal extension and/or help device selection (cutting balloon, stent) and sizing – On IVUS hematoma is difficult to differentiate from homogenous plaques
Type 3	– Mimics classic atheroma lesions due to its focality – Discrete "sole" lesions (11–20 mm) – Hazy in appearance, mimics intraluminal thrombus	– May be used to visualize intramural hematoma and/or exclude atheroma involvement
Type 4	– Total vessel occlusion – Usually involves a distal vessel segments – Sources of coronary embolism need to be suspected and excluded	– May be used to guide intervention and optimize results and/or help exclude atheroma presence and thrombotic involvement

IVUS, intravascular ultrasound; OCT, optical coherence tomography.

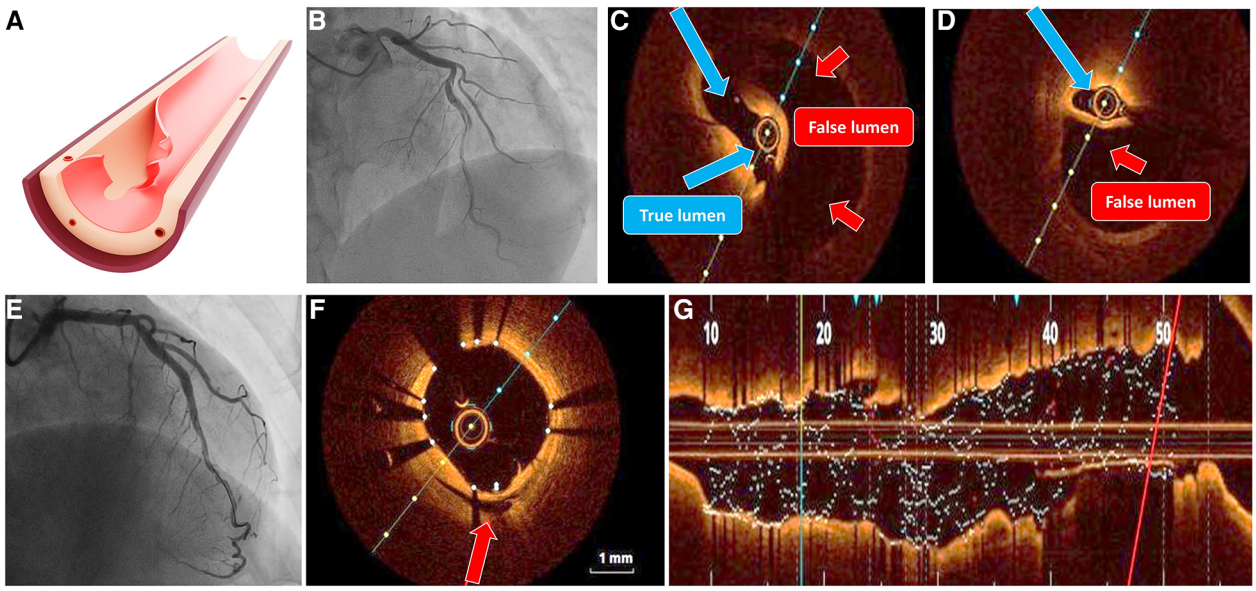


FIGURE 1
SCAD type 1. (A) Illustration of intimal tear; (B) angiographic classical radiolucent dissection line along left anterior descending artery; (C,D) OCT imaging confirming the presence of double-lumen and intimal flap (true lumen blue arrows, false lumen red arrows) without evidence of atherosclerosis or thrombosis; (E) result after long stent implantation; (F) OCT cross section showing good stent apposition with compression of false lumen (green arrow); and (G) longitudinal OCT image after optimal stent implantation, without evidence of residual dissection. OCT, optical coherence tomography.

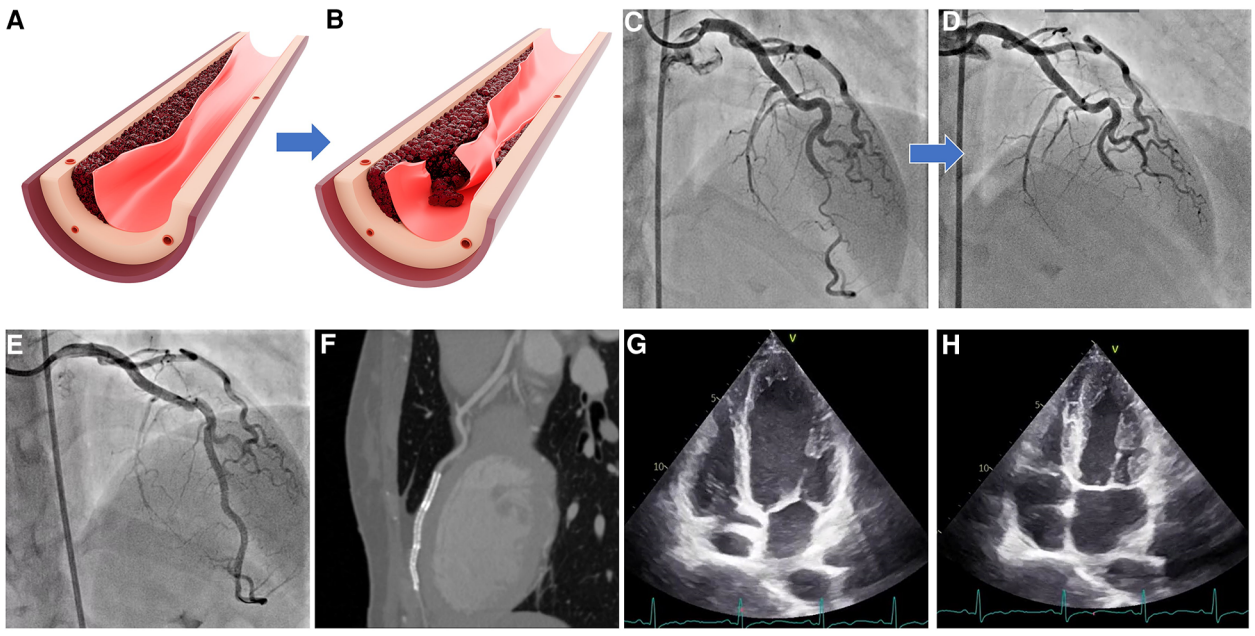


FIGURE 2
SCAD types 2 and 4. (A) Illustration of moderate intramural hematoma without intimal tear; (B) propagation of hematoma with tear causing complete vessel occlusion; (C) angiographic appearance of SCAD type 2; (D) angiographic appearance of SCAD type 4; (E) result after three long overlapping stent implantations; (F) control MSCT poststenting showing overlapping stents and no evidence of residual dissections; and (G,H) echocardiographic evidence of complete restoration of wall contractility after successful stent implantation. SCAD, spontaneous coronary artery dissection.

while type IIb lesions show complete distal vessel involvement. Differential diagnosis compromises classic atherosclerotic plaques; therefore, the probable diagnosis of SCAD type 2 should be considered in cases when there are no other atherosclerotic lesions, or when such instances occur within tortuous segments. In addition, intravascular imaging should be reserved for

ambiguous cases, particularly considering that conservative treatment is recommended in majority of cases.

If hematoma localizes in short segments (less than 20 mm), it can mimic short atherosclerotic lesions. This presents the substrate of typical type 3 SCAD. Due to extreme angiographic similarity to atherosclerotic lesion, intracoronary imaging is frequently required to make the precise diagnosis (**Figure 3C**).

SCAD type 4, newly proposed by Al-Husseini et al., compromises complete occlusion of the vessel (24). Since this is a common finding in regular ACS patients, this type presents significant challenges to be diagnosed without uncertainty. Since vessel occlusion needs to be resolved, as in classical ACS, precise diagnosis should be subsided to optimizing flow and patient patency. Alternative diagnosis can also be suspected such as thromboembolic occlusion (**Figures 2B,D**).

Importantly, although SCAD hallmark is a "sole" lesion, vessel fragility is an unlocalized feature, and simultaneous multivessel dissections can occur in approximately 10% of cases (25, 26).

Intravascular SCAD imaging modalities

Both contemporary invasive imaging modalities, OCT and IVUS, are capable of providing detailed phenomena that are characteristic of SCAD type lesions, such as existence of intimal flap, presence and length of extension of intramural hematoma, possible presence of intramural thrombus, absence of classical atherosclerosis (2, 26, 27). Thus, in addition to possessing unquestionable diagnostic value, they can also assist us in implementing the best PCI strategy (choosing the stent length, cutting balloon diameter, geographic landing location to cover the entry and/or exit site of the dissection, etc.) (28). Before deciding to use these intravascular devices, it is necessary to take into account the potential risks: extension of the dissection by the subintimal placement of the guide catheter, wire, or device itself, hydraulic extension of the false lumen with the application of contrast in the case of OCT, further unwanted compromise of flow due to a small residual circulating lumen when devices are in place, iatrogenic dissection with a catheter during manipulation (common when SCAD is associated with connective tissue weakness), etc. (**Figure 4**) (23). Therefore, imaging methods should only be used if the artery's lumen is sufficiently large, if angiographic findings are ambiguous, and/or if a further PCI approach has been determined. High operator attentiveness and clearly defined angiographic varieties of SCAD lesions help to avoid the unnecessary utilization of these modalities while preserving the degree of readiness for their rational use.

Intravascular ultrasound provides grayscale images of coronary arteries and walls by a catheter tipped with ultrasound probe (29, 30). One of the advantages of IVUS imaging is its wide availability. In addition, IVUS imaging does not require the application of contrast dye and allows sufficient circumferential field depth for visualization of even large vessels. As such, IVUS can provide valuable information regarding the proportions of the false lumen and the extent of hematoma and can show the false-true lumen separation. However, its limited spatial resolution (100–150 μM) and insufficient grayscale discrimination between homogenous areas (such as hematoma and lipid-rich atherosclerotic plaques) can result in undesirable diagnostic uncertainty, particularly when used by less experienced operators.

Optical coherence tomography is an intravascular imaging modality that uses infrared light technology to produce images with 10 times higher resolution than IVUS (29, 30). Instead of using ultrasound, the method employed near infrared light technology, which is absorbed and reflected by tissues and structures upon interaction, depending on their composition. Tissue characterization is accomplished by digital interpretation of the intensified or attenuated recaptured optical signals, even allowing precise intimal border visualization. Therefore, it is the most sensitive modality to depict false-true lumen and intramural hematomas, essential for confirming SCAD diagnosis. However, since it requires vigorous contrast dye injections, it possesses great risk for dissection enlargement. In addition, its use in real-time guide wire manipulations (when true lumen wire negotiation is attempted) is limited compared with IVUS (**Figures 4A,B**) since it has a short mode of image

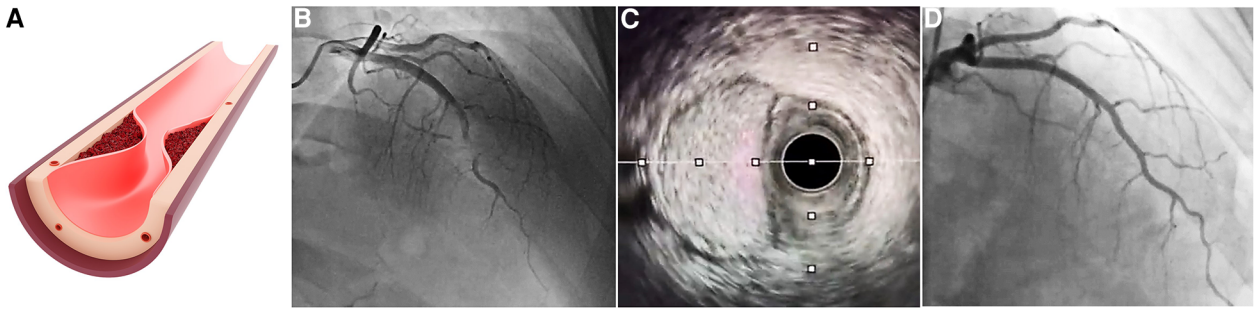


FIGURE 3
SCAD type 3. (**A**) Illustration of discrete short hematoma presence mimicking classic lesion; (**B**) angiographic appearance of SCAD type 3; (**C**) IVUS imaging showing large intramural hematoma with preserved "uncompressed" lumen; and (**D**) control angiography after hematoma resolution following conservative approach. IVUS, intravascular ultrasound; SCAD, spontaneous coronary artery dissection.

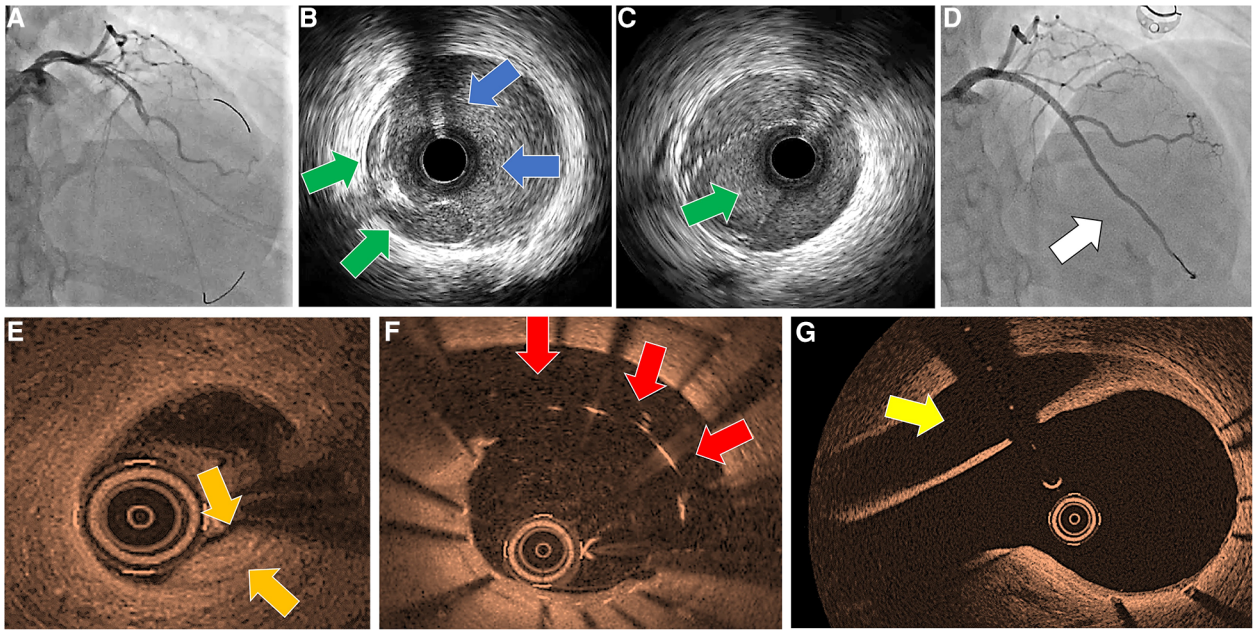


FIGURE 4
Iatrogenic dissection in an SCAD patient during invasive imaging. (**A**) First angiographic scene after catheter caused dissection of left-main artery showing distal wide-spreading of dissection; (**B**) IVUS probe in false lumen (blue arrows), showing compressed true lumen (green arrows); (**C**) IVUS probe in true lumen (green arrows); (**D**) result after overlapping stent implantations form left-main to distal left anterior descending; (**E**) control in-hospital OCT imaging showing compression of true lumen in distal artery (initial SCAD provoking substrate, compressed dissected lumen, orange arrows); (**F**) stent malapposition with persisting large dissection lumen (red arrows); (**G**) dissection lumen in left-main artery, caused by catheter engagement (yellow arrow). IVUS, intravascular ultrasound; OCT, optical coherence tomography.

recording of just approximately 2 s in the automatic pullback mode.

Non-invasive SCAD imaging modalities

Other imaging modalities, such as MSCT-CA, echocardiography, myocardial perfusion imaging (MPI), or cardiac magnetic resonance (CMR), can provide additional diagnostic information for streamlining the possible SCAD cases that can lead to coronarography and exact diagnosis (28, 31). For instance, the presence of myocardial ischemia or infarction as detected by regional wall motion abnormalities using focused echocardiography, the decreased myocardial perfusion on MPI, or the detection of myocardial infarction by late gadolinium enhancement detected by CMR can provide complementary evidence and support the diagnosis (32). According to literature, CMR can be considered in cases when SCAD is suspected to confirm the occurrence of myocardial infarction, to assess the extent of myocardial involvement, and more importantly to elucidate concurrent etiologies and sequelae (33).

The MSCT-CA is commonly employed as the initial assessment tool for low-risk patients or clinically uncertain cases, since it is widely adopted by medical facilities for non-invasive imaging in the first-line assessment of ACS patients. The advancements in spatial and temporal resolution have greatly enhanced the ability to assess the main epicardial vessels. However, the current MSCT-CA still lacks the capability to accurately assess small distal coronary arteries due to its limited resolution. There are several distinct features that can be seen on MSCT-CA that can help or even confirm the diagnosis of SCAD, including the absence of atherosclerotic plaque, tapered luminal stenosis, abrupt luminal stenosis, luminal occlusion, intramural hematoma with hemorrhage within the wall of the coronary artery, dissection flap, and perivascular epicardial fat stranding. In addition, the likelihood of SCAD can be increased in cases when there is cardiac hypoperfusion occurring in a similar vascular area. However, such findings are not specific to SCAD and are frequently observed in other acute coronary syndromes (34).

Holistic SCAD diagnostic pathway

SCAD diagnosis requires a holistic integrative approach, starting with a high level of suspicion from first-line medical professionals, due to the relatively rarity of the condition and the potential for its symptoms to mimic those of other acute conditions. Since SCAD can be life-threatening, early and accurate diagnosis is crucial for providing appropriate and timely treatment. The comprehensive diagnostic approach for SCAD begins with an assessment of preimaging probability, considering the patient's medical history, risk factors, and presenting symptoms that can streamline further diagnostic tests. By incorporating findings from various stepwise multimodality imaging techniques that can confirm possible disruption of the coronary wall integrity, treating practitioners can increase the certainty of diagnosing this relatively rare phenomenon,

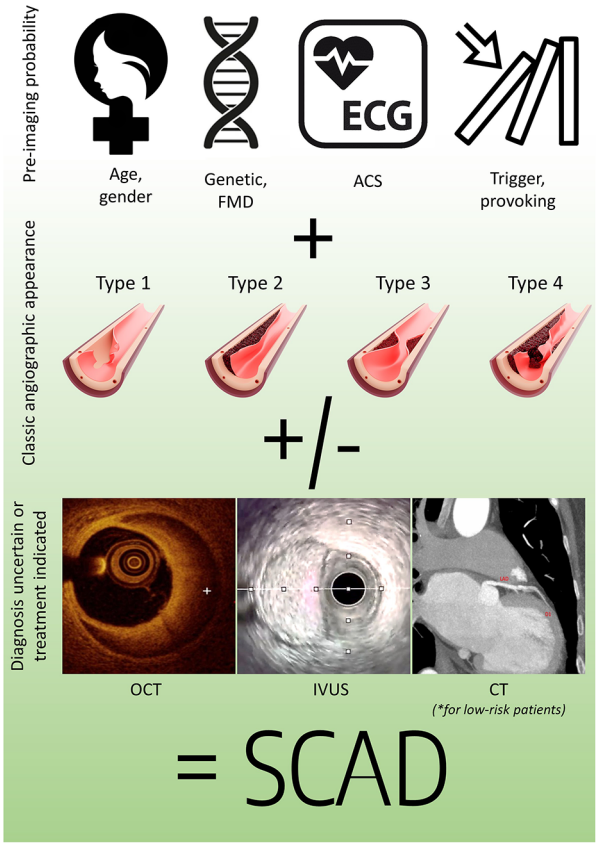


FIGURE 5
Holistic SCAD diagnostic pathway. ACS, acute coronary syndrome; CT, computed tomography; FMD, fibromuscular dysplasia; IVUS, intravascular ultrasound; OCT, optical coherence tomography.

and, most importantly, this enables them to make informed decisions regarding further treatment strategies (Figure 5) (2, 13).

Conclusion

SCAD presents rare but unique pathoanatomical lesion substrate among patients presenting with ACS. Proper diagnosis of SCAD begins with a high level of suspicion and awareness regarding the condition, which is subsequently supported by the utilization of non-invasive and invasive imaging modalities in order to initiate an appropriate treatment strategy. Accurate interpretation of various imaging modalities is crucial, not only for SCAD recognition, but also for deciding on subsequent treatment strategies.

Author contributions

ZM: Writing – original draft. II: Conceptualization, Writing – review & editing. MČ: Conceptualization, Writing – review & editing. ZP: Conceptualization, Writing – review & editing. TK: Conceptualization, Writing – review & editing. BM: Conceptualization, Writing – review & editing. GK: Conceptualization, Writing – review & editing. BB: Writing – review & editing. SA: Writing – review & editing.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Saw J, Starovoytov A, Aymong E, Inohara T, Alfadhel M, McAlister C, et al. Canadian spontaneous coronary artery dissection cohort study: 3-year outcomes. *J Am Coll Cardiol.* (2022) 80(17):1585–97. doi: 10.1016/j.jacc.2022.08.759

2. Adlam D, Alfonso F, Maas A, Vrints C, Committee W. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J.* (2018) 39 (36):3353–68. doi: 10.1093/eurheartj/ehy080

3. Waterbury TM, Tweet MS, Hayes SN, Eleid MF, Bell MR, Lerman A, et al. Early natural history of spontaneous coronary artery dissection. *Circ Cardiovasc Interv.* (2018) 11(9):e006772. doi: 10.1161/CIRCINTERVENTIONS.118.006772

4. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, et al. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the American Heart Association. *Circulation.* (2019) 139(18): e891–908. doi: 10.1161/CIR.0000000000000670

5. Ricci F, Neumann JT, Rübsamen N, Sörensen NA, Ojeda F, Cataldo I, et al. High-sensitivity troponin I with or without ultra-sensitive copeptin for the instant rule-out of acute myocardial infarction. *Front Cardiovasc Med.* (2022) 9:895421. doi: 10.3389/fcvm.2022.895421

6. Bin Saeedan M, Ramchand J, Bolen M. Role of computed tomography angiography in setting of spontaneous coronary artery dissection. *Curr Probl Diagn Radiol.* (2021) 50(4):532–9. doi: 10.1067/j.cpradiol.2020.07.010

7. García-Guimarães M, Sanz-Ruiz R, Sabaté M, Velázquez-Martín M, Veiga G, Ojeda S, et al. Spontaneous coronary artery dissection and ST-segment elevation myocardial infarction: does clinical presentation matter? *Int J Cardiol.* (2023) 373:1–6. doi: 10.1016/j.ijcard.2022.11.033

8. Gudenkauf B, Hays AG, Tamis-Holland J, Trost J, Ambinder DI, Wu KC, et al. Role of multimodality imaging in the assessment of myocardial infarction with nonobstructive coronary arteries: beyond conventional coronary angiography. *J Am Heart Assoc*. (2022) 11(1):e022787. doi: 10.1161/JAHA.121.022787

9. Lionakis N, Briasoulis A, Zouganeli V, Dimopoulos S, Kalpakos D, Kourek C. Spontaneous coronary artery dissection: a review of diagnostic methods and management strategies. *World J Cardiol*. (2022) 14(10):522–36. doi: 10.4330/wjc.v14.i10.522

10. Bocchino PP, Angelini F, Franchin L, D'Ascenzo F, Fortuni F, De Filippo O, et al. Invasive versus conservative management in spontaneous coronary artery dissection: a meta-analysis and meta-regression study. *Hellenic J Cardiol*. (2021) 62 (4):297–303. doi: 10.1016/j.hjc.2021.02.013

11. Smaardijk VR, Mommersteeg PMC, Kop WJ, Adlam D, Maas AHEM. Psychological and clinical characteristics of female patients with spontaneous coronary artery dissection. *Neth Heart J*. (2020) 28(9):485–91. doi: 10.1007/s12471-020-01437-7

12. Luong C, Starovoytov A, Heydari M, Sedlak T, Aymong E, Saw J. Clinical presentation of patients with spontaneous coronary artery dissection. *Catheter Cardiovasc Interv*. (2017) 89(7):1149–54. doi: 10.1002/ccd.26977

13. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. (2016) 133(9):916–47. doi: 10.1161/CIR.0000000000000351

14. Nishiguchi T, Tanaka A, Ozaki Y, Taruya A, Fukuda S, Taguchi H, et al. Prevalence of spontaneous coronary artery dissection in patients with acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care*. (2016) 5(3):263–70. doi: 10.1177/2048872613504310

15. Di Monaco S, Georges A, Lengelé JP, Vikkula M, Persu A. Genomics of fibromuscular dysplasia. *Int J Mol Sci*. (2018) 19(5):1526. doi: 10.3390/ijms19051526

16. Persu A, Lopez-Sublet M, Al-Hussaini A, Pappaccogli M, Radhouani I, Van der Niepen P, et al. Prevalence and disease spectrum of extracoronary arterial abnormalities in spontaneous coronary artery dissection. *JAMA Cardiol*. (2022) 7 (2):159–66. doi: 10.1001/jamacardio.2021.4690

17. Combaret N, Gerbaud E, Dérimay F, Souteyrand G, Cassagnes L, Bouajila S, et al. National French registry of spontaneous coronary artery dissections: prevalence of fibromuscular dysplasia and genetic analyses. *EuroIntervention*. (2021) 17(6):508–15. doi: 10.4244/EIJ-D-20-01046

18. Fahmy P, Prakash R, Starovoytov A, Boone R, Saw J. Pre-disposing and precipitating factors in men with spontaneous coronary artery dissection. *JACC Cardiovasc Interv*. (2016) 9(8):866–8. doi: 10.1016/j.jcin.2016.02.024

19. Havakuk O, Goland S, Mehra A, Elkayam U. Pregnancy and the risk of spontaneous coronary artery dissection: an analysis of 120 contemporary cases. *Circ Cardiovasc Interv*. (2017) 10(3). doi: 10.1161/CIRCINTERVENTIONS.117.004941

20. Tweet MS, Miller VM, Hayes SN. The evidence on estrogen, progesterone, and spontaneous coronary artery dissection. *JAMA Cardiol*. (2019) 4(5):403–4. doi: 10.1001/jamacardio.2019.0774

21. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. *Catheter Cardiovasc Interv*. (2014) 84(7):1115–22. doi: 10.1002/ccd.25293

22. Motreff P, Malcles G, Combaret N, Barber-Chamoux N, Bouajila S, Pereira B, et al. How and when to suspect spontaneous coronary artery dissection: novel insights from a single-centre series on prevalence and angiographic appearance. *EuroIntervention*. (2017) 12(18):e2236–e43. doi: 10.4244/EIJ-D-16-00187

23. Prakash R, Starovoytov A, Heydari M, Mancini GB, Saw J. Catheter-induced iatrogenic coronary artery dissection in patients with spontaneous coronary artery dissection. *JACC Cardiovasc Interv*. (2016) 9(17):1851–3. doi: 10.1016/j.jcin.2016.06.026

24. Al-Hussaini A, Adlam D. Spontaneous coronary artery dissection. *Heart*. (2017) 103(13):1043–51. doi: 10.1136/heartjnl-2016-310320

25. Salamanca J, García-Guimarães M, Sabaté M, Sanz-Ruiz R, Macaya F, Roura G, et al. Multivessel spontaneous coronary artery dissection: clinical features, angiographic findings, management, and outcomes. *Int J Cardiol*. (2023) 370:65–71. doi: 10.1016/j.ijcard.2022.11.011

26. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation*. (2018) 137(19): e523–57. doi: 10.1161/CIR.0000000000000564

27. Saw J, Mancini GB, Humphries K, Fung A, Boone R, Starovoytov A, et al. Angiographic appearance of spontaneous coronary artery dissection with intramural hematoma proven on intracoronary imaging. *Catheter Cardiovasc Interv*. (2016) 87 (2):E54–61. doi: 10.1002/ccd.26022

28. Marrazzo G, Palermi S, Pastore F, Ragni M, De Luca M, Gambardella M, et al. Multimodality imaging approach to spontaneous coronary artery dissection. *J Clin Med*. (2022) 12(1):154. doi: 10.3390/jcm12010154

29. Johnson TW, Räber L, di Mario C, Bourantas C, Jia H, Mattesini A, et al. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. (2019) 40(31):2566–84. doi: 10.1093/eurheartj/ehz332

30. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. (2018) 39(35):3281–300. doi: 10.1093/eurheartj/ehy285

31. Tweet MS, Gulati R, Williamson EE, Vrtiska TJ, Hayes SN. Multimodality imaging for spontaneous coronary artery dissection in women. *JACC Cardiovasc Imaging*. (2016) 9(4):436–50. doi: 10.1016/j.jcmg.2016.01.009

32. Krljanac G, Apostolovic S, Mehmedbegovic Z, Nedeljkovic-Arsenovic O, Maksimovic R, Ilic I, et al. Chronic or changeable infarct size after spontaneous coronary artery dissection. *Diagnostics*. (2023) 13(9):1518. doi: 10.3390/diagnostics13091518.

33. Tan NY, Hayes SN, Young PM, Gulati R, Tweet MS. Usefulness of cardiac magnetic resonance imaging in patients with acute spontaneous coronary artery dissection. *Am J Cardiol*. (2018) 122(10):1624–9. doi: 10.1016/j.amjcard.2018.07.043

34. Capretti G, Mitomo S, Giglio M, Colombo A, Chieffo A. Spontaneous coronary artery dissection: how often do we miss this diagnosis? The role of cardiac computed tomography angiography. *Future Cardiol*. (2019) 15(5):333–8. doi: 10.2217/fca-2018-0089

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 20 October 2023
DOI 10.3389/fcvm.2023.1260478

OPEN ACCESS

EDITED BY
Artur Dziewierz,
Jagiellonian University Medical College, Poland

REVIEWED BY
Sridevi Pitta,
Texas Christian University, United States
Jacek Kadziela,
National Institute of Cardiology, Poland

*CORRESPONDENCE
Aleksandra Djokovic
✉ drsaska@yahoo.com

RECEIVED 17 July 2023
ACCEPTED 09 October 2023
PUBLISHED 20 October 2023

CITATION
Djokovic A, Krljanac G, Matic P, Zivic R, Djulejic V, Marjanovic Haljilji M, Popovic D, Filipovic B and Apostolovic S (2023) Pathophysiology of spontaneous coronary artery dissection: hematoma, not thrombus. Front. Cardiovasc. Med. 10:1260478. doi: 10.3389/fcvm.2023.1260478

Pathophysiology of spontaneous coronary artery dissection: hematoma, not thrombus

Aleksandra Djokovic[1,2]*, Gordana Krljanac[1,3], Predrag Matic[1,4], Rastko Zivic[1,5], Vuk Djulejic[1,6], Marija Marjanovic Haljilji[7], Dusan Popovic[1,7], Branka Filipovic[1,7] and Svetlana Apostolovic[8,9]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Serbia, [2]Department of Cardiology, University Hospital Center Bezanijska Kosa, Belgrade, Serbia, [3]Cardiology Clinic, University Clinical Center of Serbia, Belgrade, Serbia, [4]Clinic for Vascular Surgery, Institute for Cardiovascular Diseases "Dedinje", Belgrade, Serbia, [5]Department for Surgery, Clinical Hospital Center Dr Dragisa Misovic "Dedinje", Belgrade, Serbia, [6]Faculty of Medicine, Institute of Anatomy, Belgrade, Serbia, [7]Department for Gastroenterology, Clinical Hospital Center Dr Dragisa Misovic "Dedinje", Belgrade, Serbia, [8]Coronary Care Unit, Cardiology Clinic, University Clinical Center of Nis, Nis, Serbia, [9]Faculty of Medicine, University of Nis, Nis, Serbia

Spontaneous coronary artery dissection (SCAD) accounts for 1.7%–4% of all acute coronary syndrome presentations, particularly among young women with an emerging awareness of its importance. The demarcation of acute SCAD from coronary atherothrombosis and the proper therapeutic approach still represents a major clinical challenge. Certain arteriopathies and triggers are related to SCAD, with high variability in their prevalence, and often, the cause remains unknown. The objective of this review is to provide contemporary knowledge of the pathophysiology of SCAD and possible therapeutic solutions.

KEYWORDS

spontaneous coronary artery dissection, acute coronary syndrome, pathophysiology, women's health, pregnancy, fibromuscular dysplasia

1. Introduction

Spontaneous coronary artery dissection (SCAD) is an often-underrecognized clinical condition primarily associated with acute coronary syndrome (ACS) in young or middle-aged women, which can have fatal consequences. The utilization of intracoronary imaging techniques and the introduction of an angiographic classification by Saw J et al. in 2014 (1), as well as SCAD position papers published by the European Society of Cardiology and American Heart Association in 2018 (2, 3), have contributed to the increased recognition and prevalence of SCAD. In the USA, the estimated prevalence of SCAD in ACS ranges from 1.7% to 4% (4), while it varies from 3.1% to 9.7% in patients with premature myocardial infarction (less than 45 years) (5–7), and up to 43% in females experiencing ACS during the peripartum period (8). A meta-analysis of 2,172 SCAD patients conducted by Franke KB et al. reported that 84% of the cases involved females, with a mean age of 51 years, and significant heterogeneity across studies regarding baseline characteristics and outcomes analyzed (9). While the majority of patients typically present with characteristic chest pain (96%) and show elevated cardiac biomarkers (10), a small subset (0.4%–4%) may exhibit normal cardiac troponin levels (11). Additionally, SCAD has been identified as a potential cause of sudden cardiac death (SCD) in 3%–11% of cases, which raises the possibility of an underestimation of SCAD prevalence. This observation highlights the challenge in accurately assessing SCAD's true frequency, particularly given the limited data available

from postmortem cases (4). Timely diagnosis of SCAD is crucial due to its distinct pathophysiology and management compared to atherosclerotic disease.

2. Anatomy and physiology of coronary arteries

Coronary arteries arise from the aortic root, which is the initial segment of the ascending aorta. The right coronary artery (RCA) originates from the right sinus of Valsalva and enters the atrioventricular groove, descending anteriorly and inferiorly along the right border of the heart, giving rise to several branches before passing posteriorly and inferiorly (12). The left coronary artery, the main stem, originates from the left sinus of Valsalva, travels anteriorly and to the left between the left atrial appendage and the pulmonary trunk, dividing shortly into the circumflex (Cx) and anterior interventricular (or descending) (LAD) arteries (13, 14). Although coronary vessels were traditionally considered branches of the aorta, recent studies on mouse models have shown that coronary arteries derive from cells originating from the sinus venosus, the venous inflow tract of the primitive heart. These cells migrate to the muscle layer and form a vascular plexus that subsequently remodels into arteries (15). The vascular supply of arteries larger than 0.5 mm is provided by vasa vasorum, which traverse the adventitia but not the muscular layer of the vessel wall due to luminal compressive forces. Vasa vasorum can be classified into vasa vasorum interna, originating from the luminal surface or media and penetrating the vessel wall toward the adventitia, and vasa vasorum externa, primarily located in the adventitia and originating from various anatomical points (16).

The adventitia represents a vital component of the vessel wall, regulating the inflammatory response and contributing to vessel repair. However, its impaired ability to respond adequately to injury is implicated in both spontaneous dissection and atherosclerotic processes (17). In a study analyzing the mechanical properties of coronary arteries *in vitro*, Claes E et al. investigated five human donors. They found that the responsiveness of coronary arteries to wall stress follows a typical J-curve pattern, with the initial portion dependent on elastin and the stiffer segment reliant on collagen. This relationship may shift upward over time due to aging or distinct pathologies. While coronary arteries are considered elastic, their circumferential strength is significantly lower than that of the aorta and declines progressively with age, with a more pronounced decrease occurring around the ages of 30–40 years (18).

The pressure within the internal vasa vasorum is lower than that in the coronary artery, supported by the firmness and elasticity of the endothelium. However, when the endothelium becomes infiltrated with inflammatory cells and cytokines, it becomes compromised, leading to vessel wall disruption and the transmission of pressure from the coronary artery lumen to the subintimal layer (16).

3. Definition and classification of SCAD

The first autopsy report on SCAD was published in 1931 (19). Since then, there has been increasing recognition of SCAD, leading to numerous publications in the past decade and highlighting the need for a precise definition of this condition. SCAD is currently defined as the spontaneous tearing of the coronary artery wall, resulting in the formation of an intimal hematoma that obstructs blood flow. It is important to note that the term SCAD specifically excludes iatrogenic dissections (those induced by medical procedures) and those associated with trauma. Additionally, the contemporary definition of SCAD excludes cases involving atherosclerotic coronary artery disease.

Initially, SCAD was classified into four angiographic types (1) (**Figure 1**). Type 1 is considered pathognomonic, characterized by contrast staining of the coronary artery wall and the presence of a false lumen. Type 2 SCAD is often misdiagnosed as it presents as a diffusely narrowed segment, commonly involving the medial or distal parts of the artery, with a subtle demarcation line separating it from the true caliber of the coronary artery. Type 2 SCAD is further divided into Type 2A, where normal arterial segments can be observed proximal and distal to the SCAD segment, and Type 2B, where the dissection extends to the distal tip of the artery (20). Type 3 SCAD is challenging to diagnose due to its focal appearance. More recently, Type 4 SCAD was added to the classification, characterized by total occlusion of the vessel, which must be differentiated from a thromboembolic event (21). Tanis et al. proposed an alternative classification based on the etiology of SCAD, dividing it into four subtypes: peripartum, atherosclerotic, idiopathic, and those related to connective tissue disorders (22).

4. Proposed mechanisms of SCAD

The etiology and pathophysiology of SCAD still present many unresolved questions. The existence of two types of SCAD—one with an intimal tear and blood entering the vessel wall ("inside-out"), and the other without an observed intimal tear, hypothesized as a consequence of vasa vasorum rupture ("outside-in")—complicates our understanding of the underlying cause of this condition (20) (**Figure 2**). In an observational study of 65 SCAD patients, optical coherence tomography (OCT) was utilized to investigate false lumen formation (23). The absence of fenestration in the false lumen results in increased pressure, leading to compression of the true lumen. The authors proposed that the "outside-in" theory may unify the pathophysiology of SCAD. However, the lack of studies supporting the hypothesis of intramural bleeding with subsequent false lumen formation keeps the "inside-out" theory alive. Furthermore, the theory that intimal hemorrhage generates enough pressure to compromise flow in the true lumen requires further investigation through mechanical stress studies (24). An OCT study by Kwon et al. reported a higher density of adventitial vasa vasorum in SCAD

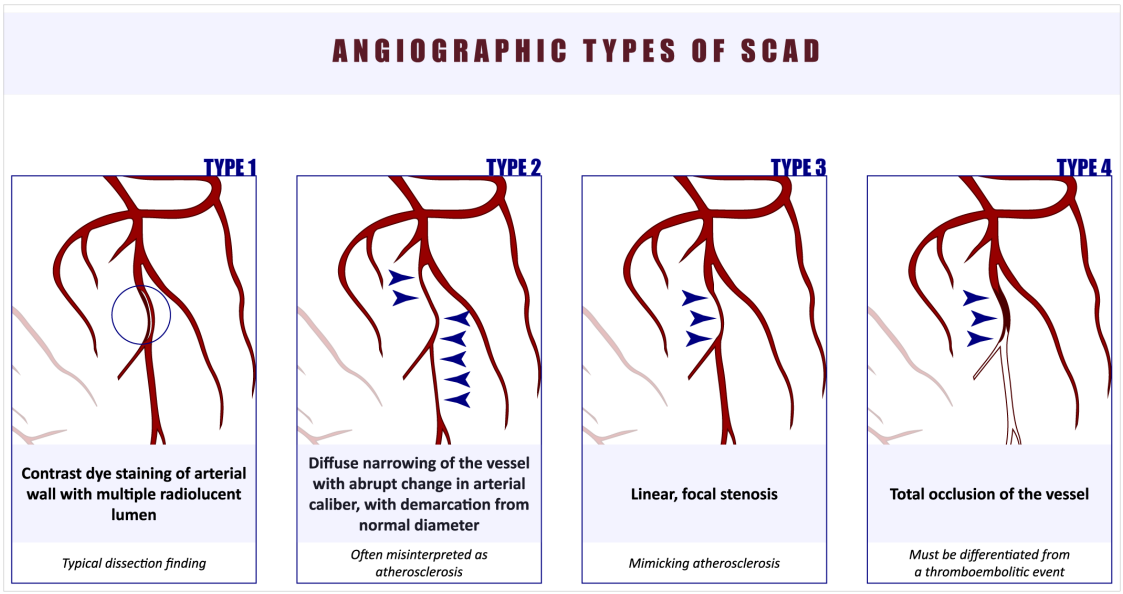


FIGURE 1
Four different angiographic types of SCAD.

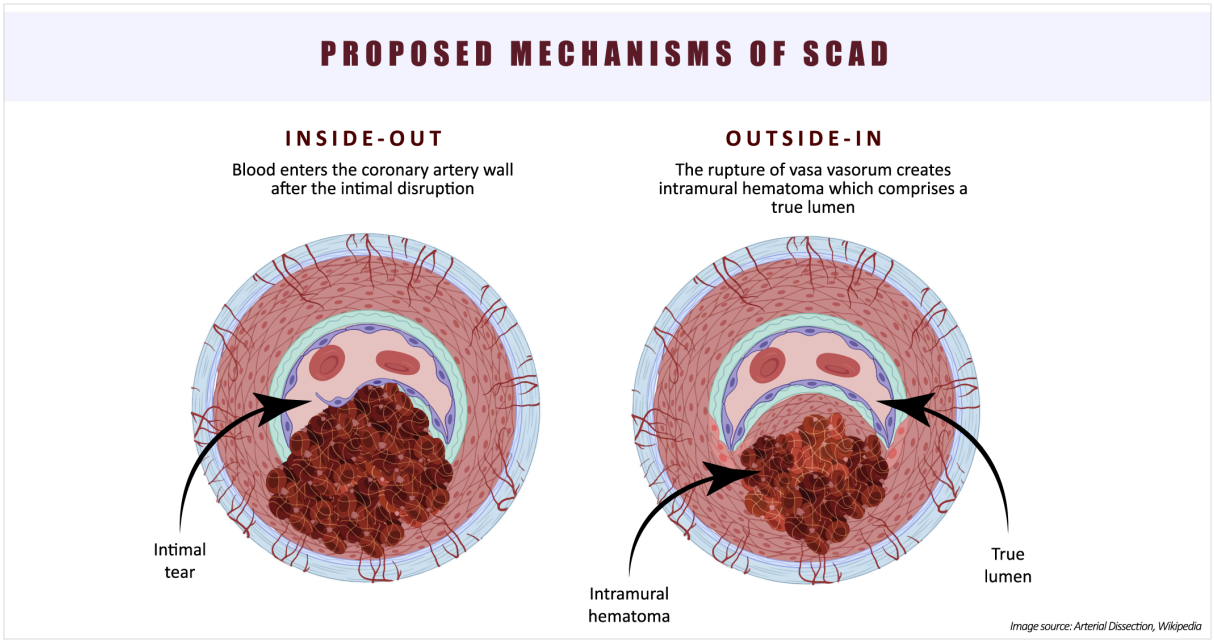


FIGURE 2
Proposed mechanisms of SCAD occurrence.

patients compared to those with non-obstructive atherosclerotic coronary artery disease (CAD), suggesting that this anatomical feature may contribute to the occurrence of SCAD (25).

The role of microvasculature in the pathophysiology of SCAD remains unclear. It is reasonable to assume that microvascular dysfunction, which has been implicated in various cardiovascular diseases, plays a role in the pathophysiology of SCAD as well. However, specific studies addressing this aspect are currently lacking.

Inflammation and abnormalities of connective tissue have been proposed as important factors in the pathophysiology of SCAD (26). Autopsy reports frequently describe infiltration of the adventitia surrounding SCAD with inflammatory cells, although the true relationship has not been proven or well understood

(27). Based on autopsy study findings, segmental eosinophilic infiltration has been identified as a pathognomonic feature of non-atherosclerotic SCAD (28). A small retrospective study by Canga et al. reported significantly higher levels of systemic inflammation markers (white blood cell count, neutrophil-to-lymphocyte ratio, C-reactive protein) in SCAD patients compared to controls, similar to patients with CAD, but the causal relationship between inflammation and SCAD remains uncertain (29). The perivascular adipose tissue attenuation around coronary arteries, as determined by coronary computed tomography angiography (CCTA), represents a novel imaging marker for assessing inflammation burden. In a recent study, it was discovered that 48 SCAD patients exhibited higher pericoronary adipose tissue attenuation when compared to patients without SCAD, indicating an elevated perivascular inflammatory activity within this patient population (30).

A study by Margarits M et al. compared the coronary and myocardial histology and immunohistochemistry findings of 36 autopsy SCAD cases with 359 SCAD survivors (31). Autopsy cases were predominantly characterized by single-vessel disease, with a higher proportion involving the left main artery. Two-thirds of autopsy cases did not develop myocardial infarction. Inflammation was more pronounced in the dissected region, suggested to be a reaction rather than the cause of SCAD, and was more intensively present in SCAD survivors. Approximately 47% of autopsy cases exhibited limited intimal fibro-elastic thickening without features of fibromuscular dysplasia (FMD) or abnormalities in the endothelial or internal elastic lamina. There were no differences in vasa vasorum density between SCAD cases and controls.

The genetic predisposition for SCAD is not yet fully understood. Genetic studies indicate that a small percentage of SCAD patients carry distinct gene mutations (32). Additionally, SCAD occurs frequently in patients with FMD and migraine, and recent genetic studies have identified shared risk variants between these conditions and SCAD (33). In a meta-analysis comprising 1,917 cases and 9,292 controls, Adlam et al. identified 16 risk loci for SCAD, primarily associated with genes involved in vascular muscle cells and fibroblasts (34). Based on a specific risk locus for factors initiating coagulation, the authors concluded that arterial integrity, along with tissue-mediated coagulation, should be considered in the pathophysiology of SCAD, opening up new possibilities for management and prevention. The shared genetics found between hypertension and SCAD also suggest the need for future studies on possible similar biological pathways in SCAD and CAD.

4.1. Hormonal influences and SCAD

Appreciating the fact that the typical SCAD patient is a woman aged between 44 and 53 years, it is reasonable to assume that sex hormones play an important role in SCAD pathophysiology.

Data from the SWED-PREG registry, which includes women diagnosed with SCAD between 1997 and 2019 and under 50 years of age, revealed that 28% of cases were associated with pregnancy (during pregnancy or within 14 weeks postpartum) (35). Significant changes occurring during this period are thought to contribute to the pathophysiology of SCAD. Hemodynamic, respiratory, and metabolic changes lead to a substantial increase in blood volume, placing high demands on the cardiovascular system and causing cardiomyocytes to change their elasticity and contractility (36). Additionally, vascular overload during pregnancy can induce changes in the endothelium, increasing its permeability and reducing coagulability (37). These changes occur early in pregnancy, as the placenta begins producing various molecular signals such as hormones and growth factors, which affect the peripheral vasculature (38). Hormonal changes during pregnancy weaken the media layer of the vessel wall due to decreased collagen production and alterations in collagen metabolism. In the past, it was speculated that higher levels of progesterone cause the loss of elastic fibers, making blood vessels during pregnancy more susceptible to dissection, particularly in response to high cardiac output and smooth muscle cell hypertrophy (39). However, these generalized vascular changes have not been conclusively proven in postmortem studies (40). During labor and delivery, cardiac output increases, and shear stress on the vessels rises significantly, further increasing the risk of SCAD development (41). As a result, SCAD is most commonly observed in the third trimester or postpartum period among causes of acute myocardial infarction (AMI) during pregnancy (42).

The potential for SCAD recurrence during subsequent pregnancies, often with serious consequences, necessitates clear guidance for peripartum SCAD survivors. In a cohort study involving 54 females who experienced pregnancy-associated SCAD, 15% encountered a recurrent SCAD event within a 5-year follow-up period, with 50% of these recurrences happening within 3 months after delivery (43). More recently, within a cohort of 636 women of childbearing age, 23 chose to become pregnant following a prior SCAD episode. Remarkably, most of these women managed pregnancy and lactation without any evidence of an increased risk of SCAD recurrence compared to women with a history of SCAD who did not become pregnant (44). Furthermore, in a meta-analysis involving 4,206 SCAD patients, pregnancy did not exhibit a significant association with recurrent SCAD (45).

While it might initially appear reasonable to advise peripartum SCAD survivors to avoid future pregnancies due to the unpredictable nature of SCAD (46), this recommendation is not aligned with the current consensus among experts (3). This is primarily because the majority of these patients proceed to have uncomplicated pregnancies. Instead, the recommended approach is to offer comprehensive pre-conception counseling, encouraging close collaboration between gynecologists, obstetricians, and cardiologists.

Data regarding the association between hormone replacement therapy (HRT) and oral contraceptives with SCAD are scarce. In a case report from 2011, Zehir et al. described a 36-year-old woman with a history of 7 years of third-generation oral contraceptive use who presented with AMI due to left anterior descending artery dissection and proximal thrombotic occlusion of the right coronary artery (47). Changes in the architecture of

the coronary artery wall caused by estrogen have been previously discussed as a possible explanation for the increased risk of SCAD. Oral contraceptives could potentially contribute to SCAD risk through their effects on coagulability, vasomotor control, and oxidative stress. However, in a prospective study of non-atherosclerotic SCAD patients by Saw et al., the prevalence of oral hormonal therapy use was 10.7%, without a significant causative effect (48). In the aforementioned study by Tweet et al., there was no significant difference in the prevalence of previous hormonal therapy between pregnancy-related and non-pregnancy-related SCAD patients, with rates of administration being 28% and 16%, respectively (43).

Two cases of SCAD in young females were reported in 2003, both occurring during the menstrual period (49). The authors speculated that the drop in estrogen and progesterone levels, similar to the peripartum period, triggers the loss of hormonal vascular smooth muscle cell suppression and increases smooth muscle activity, leading to coronary media frailty.

If we accept that estrogen and progesterone contribute to vessel wall weakness and predispose individuals to SCAD, it would be reasonable to assume that menopausal women without HRT are at lower risk for SCAD. In a study comparing clinical features, angiographic findings, management, and in-hospital outcomes of 245 women with SCAD based on their menopausal status, it was found that premenopausal women with SCAD had a higher clinical and angiographic risk profile, including a higher prevalence of more proximal localization and larger infarct size, leading to a higher prevalence of left ventricular systolic dysfunction (50). In contrast, postmenopausal women had a higher prevalence of standard atherosclerotic risk factors. However, there were no significant differences in terms of in-hospital major adverse cardiovascular events (MACE) between the groups.

Finally, there is limited data on a possible association between hypothyroidism and SCAD. Observations that individuals with hypothyroidism tend to have a higher prevalence of spontaneous dissections, primarily in the aortic, carotid, and vertebral arteries, have led to speculation that it may be related to SCAD as well. Patients with hypothyroidism are also more susceptible to iatrogenic SCAD. In a recent observational multicenter study of 73 SCAD patients, a significantly higher rate of hypothyroidism was observed compared to matched controls with atherosclerotic acute coronary syndrome and no evidence of coronary artery dissection (51). Possible pathways for the development of SCAD in hypothyroidism involve interstitial fluid retention and increased production of hyaluronic acid by fibroblasts, leading to the repression of smooth muscle cells and resulting in a weaker vessel wall. However, these speculations require further study and clearer demonstration in future research.

4.2. Connective tissue disorders and SCAD

Genetic studies of SCAD survivors have reported the identification of mutations associated with Marfan syndrome and Ehlers-Danlos syndrome in previously undiagnosed cases (52). In a large prospective multicenter study of 750 SCAD patients, the prevalence of connective tissue disorders (CTDs) was found to be 3.6%, and they were identified as independent predictors of 30-day major adverse cardiovascular events (27). CTDs, such as Ehlers-Danlos syndrome, Marfan syndrome (MFS), Autosomal Dominant Polycystic Kidney Disease, Loeys-Dietz syndrome, and Pseudoxanthoma elasticum, are rare hereditary conditions, and SCAD might be the initial presentation of an underlying connective tissue disorder (53). These disorders share a common feature of inadequate structure and synthesis of the extracellular matrix, as well as alterations in elastic fibers, contributing to their multisystemic nature. In fact, there are thirty-six different clinical entities, involving more than 40 different genes or gene loci, that should be differentiated from the most well-known condition, Marfan syndrome (MFS) (54).

Genetic studies, as well as cellular and molecular investigations of SCAD, have revealed disruptions in tumor growth factor beta (TGF-β) signaling, changes in the extracellular matrix, cytoskeleton, and metabolism caused by specific gene mutations, including LRP1, collagen genes, fibrillin, and TGF-β receptors. These genetic mutations are shared between many connective tissue disorders and SCAD (55).

Given that SCAD may be the initial manifestation of an underlying connective tissue disorder, it is important to include genetic testing for CTDs in the diagnostic algorithm for SCAD. Furthermore, it can be speculated that all SCAD patients are actually individuals with unrecognized connective tissue disorders, with genetic mutations expressed in female patients, who develop dissections in the presence of precipitating factors.

4.3. Fibromuscular dysplasia and SCAD

In addition to being a typical event in females, SCAD is often considered a severe manifestation of underlying systemic arteriopathy, with FMD emerging as a synonymous condition for SCAD.

FMD, a non-inflammatory and non-atherosclerotic disease of unknown etiology, was first described in 1958 by McCormack et al. in patients with renovascular hypertension (56). Initially considered hyperplasia, further studies reclassified it as dysplasia. Typical angiographic findings of FMD include two types: multifocal stenoses with "string of beads" appearance and focal lesions, primarily observed in renal and cranial vessels. Pathological classification of FMD into intimal, medial, and perimedial disease is based on the location of irregularly arranged mesenchymal cells within a loose matrix of subendothelial connective tissue and a fragmented internal elastic lamina (57). In modern practice, the diagnosis of FMD is primarily achieved through imaging techniques, rendering the pathological classification obsolete in routine clinical use. It's important to highlight that, in addition to dissection, typical clinical FMD phenotypes encompass aneurysms and marked tortuosity in the affected arteries.

One of the early studies on FMD of coronary arteries was a case series by Pate et al. in 2005, reporting seven patients with

previously documented renal FMD and typical angiographic findings of diffuse obliterative changes in middle or distal segments, predominantly in the LAD, with a clear demarcation line from the apparently healthy proximal segment (58). Prior to this study, coronary FMD was primarily diagnosed through autopsies, making this report unique in its assumption of specific angiographic findings for a condition that was considered a histopathological diagnosis. Another case series by Saw et al. in 2012 was the first to study SCAD in coronary FMD, reporting six females presenting with ACS (59). In the same year, a retrospective single-center cohort study of 87 SCAD patients reported the presence of FMD in iliac arteries in eight patients and carotid FMD in two additional patients (60).

The high prevalence of FMD in SCAD patients clearly establishes a connection between the two conditions, primarily based on the understanding that the histopathological features of FMD weaken vessel walls, making them prone to dissection in the presence of precipitating factors. Indeed, the prevalence of FMD in non-atherosclerotic SCAD patients has been found to be over 70% (48).

The occurrence of extra-coronary vascular abnormalities in SCAD patients with FMD ranges from 10% to 86%, raising important questions regarding diagnostic algorithms following a SCAD event (2). In a case series study involving 173 SCAD patients, the research focused on analyzing the prevalence of aneurysms, dissections, and tortuosity in extracoronary arteries (61). The findings revealed that 32% of patients exhibited FMD, 8% had aneurysms, and 2% experienced dissections. Interestingly, there was a comparable prevalence of arterial tortuosity between the SCAD cases and the control group, and extracoronary vascular events were rare over a median 5-year follow-up period. Identifying such extra-coronary involvement and implementing appropriate preventive measures, especially for women planning pregnancy, is of utmost importance. Unfortunately, there is no clear consensus on the design of such measures, leaving clinicians to recommend the avoidance of known precipitating factors for SCAD, such as intense exercise, emotional stress, labor and delivery, intense Valsalva-type activities, drug abuse, and intense hormonal therapy in SCAD survivors.

4.4. SCAD in systemic autoimmune diseases

Systemic autoimmune diseases, especially systemic lupus erythematosus (SLE), have been suggested to potentially contribute to the pathogenesis of SCAD. The connection between inflammation and SCAD, as discussed in previous sections, remains a subject of debate. It's uncertain whether inflammation acts as a causal factor or is simply an expected response to an intimal tear or intramural hemorrhage. Randomized trials are lacking to definitively establish the relationship and associated risks between SCAD and systemic autoimmune diseases.

Saw et al. reported that within a cohort of 168 SCAD patients, 8.9% had concomitant systemic inflammatory conditions, including ulcerative colitis, Crohn's disease, rheumatoid arthritis, celiac disease, and Graves disease (48). A systematic literature review and meta-analysis by Ullah et al. identified only 10 cases of SCAD related to systemic autoimmune diseases, with 70% of these patients having SLE. These cases predominantly presented as non-ST-elevation myocardial infarctions (NSTEMI) and exhibited a higher-than-expected rate of percutaneous coronary intervention (PCI) with overall satisfactory outcomes (62). In a large Canadian cohort analysis of 750 SCAD patients, a 4.7% prevalence of systemic inflammatory conditions was observed (27).

However, in a case-control study involving 114 SCAD cases, systemic autoimmune diseases appeared to have a similar prevalence in SCAD patients compared to controls. This study did not reveal any significant relationship between systemic autoimmune diseases and SCAD, suggesting that SCAD may not have an inflammatory basis and that routine screening for systemic autoimmune diseases may be unnecessary (63).

It's important to note that the existing literature on the relationship between SCAD and systemic autoimmune disorders is limited and primarily comprises case reports and observational studies, making it difficult to draw definitive conclusions. Future prospective studies that investigate various systemic autoimmune disorders and explore autoantibody interactions with vessel wall structures as potential causes of SCAD will offer more insights into this possible pathophysiological pathway. Notably, a recent case-control study by Civieri et al. reported a significantly higher prevalence of autoantibodies targeting angiotensin-II receptor type 1 and endothelin-1 receptor type A in SCAD patients compared to controls (including healthy individuals and those with atherosclerotic CAD), emphasizing the potential role of autoimmunity in SCAD pathophysiology (64).

The proposed pathophysiology of SCAD is summarized in **Figure 3**.

5. Clinical presentation and diagnosis of SCAD

SCAD remains an underdiagnosed condition, and many patients may not present to medical services due to mild symptoms or SCD as the first manifestation. Among those who do present, a majority present with ACS, with 26%–55% presenting as ST-elevation myocardial infarction (STEMI) (48, 65). Typical chest pain is reported in 60%–90% of cases (66). However, some cases may be asymptomatic or have minimal symptoms, leading to delayed diagnosis or misinterpretation of angiographic findings (10).

Angiographic findings are crucial for the diagnosis of SCAD, and the classification proposed by Saw et al. is often used (1). However, there can be a misinterpretation of Type 3 SCAD as atherosclerotic CAD. Simultaneous multivessel dissection may occur in 10% of cases, emphasizing the need for careful evaluation of all coronary arteries. SCAD patients also have a higher prevalence of significant coronary artery tortuosity compared to the general population, which may be related to the presence of FMD and a higher risk of recurrence (67).

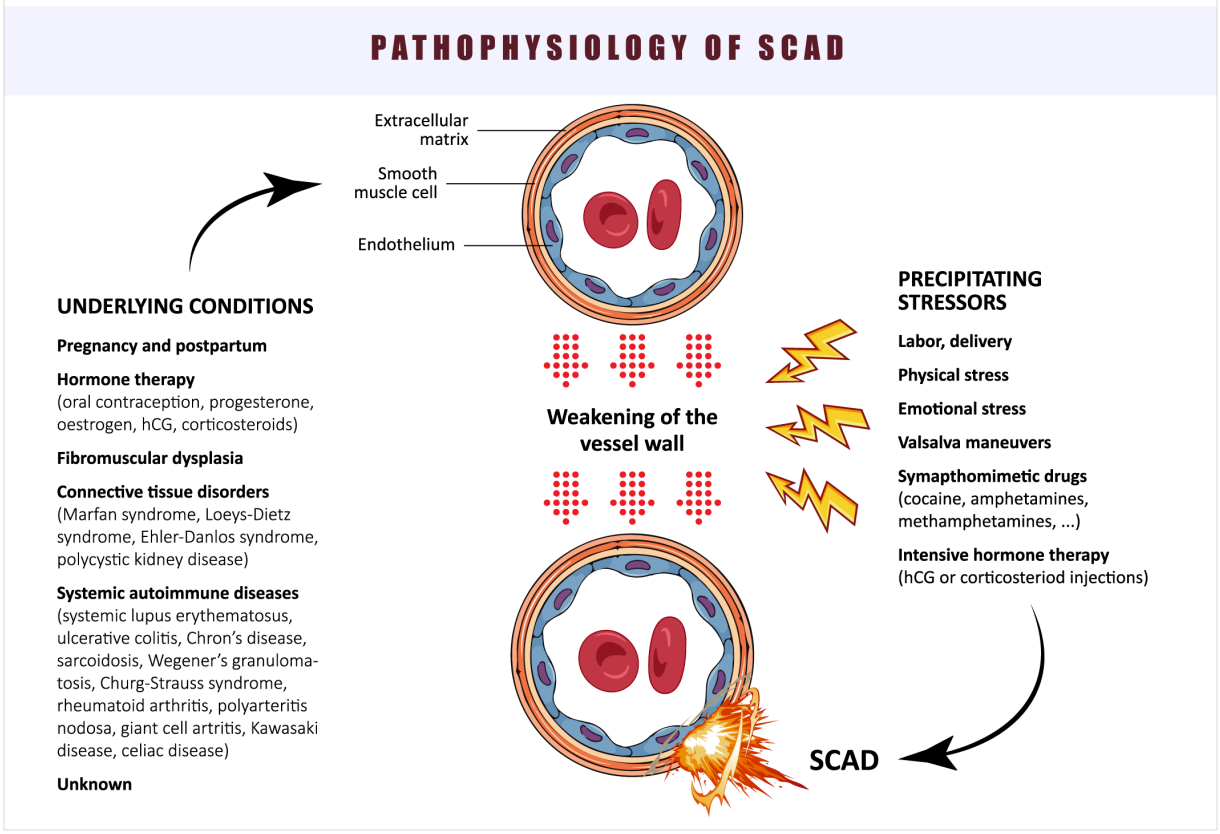


FIGURE 3
Pathophysiology of SCAD.

Intracoronary imaging techniques such as intravascular ultrasound (IVUS) and OCT have expanded our understanding of SCAD (68, 69). IVUS allows for the visualization of true and false lumens and the extension of intramural hematoma, while OCT provides high-resolution images of the vessel wall structure, location of intimal tear, and intramural hematoma size (70–72). These imaging modalities are particularly useful during percutaneous coronary intervention (PCI) to guide wire placement and stent sizing.

While non-invasive diagnostic tools for SCAD have their merits, their utility is somewhat limited. Echocardiography offers the ability to assess regional wall kinetics and left ventricular ejection fraction. On the other hand, cardiac magnetic resonance (CMR) imaging serves as a valuable tool for confirming SCAD or distinguishing it from other conditions, such as myocarditis or Takotsubo cardiomyopathy in type 4 SCAD (73, 74). However, it's important to note that normal CMR findings do not definitively rule out SCAD. CCTA, while less commonly employed in SCAD diagnosis, may find a role in follow-up due to its non-invasive nature and lower risk of catheter-induced injury. Nevertheless, interpreting CCTA findings can pose challenges, as intramural hematomas can sometimes be mistaken for artifacts, and non-calcified atherosclerotic plaques might be inaccurately interpreted as SCAD.

In summary, SCAD diagnosis relies on angiographic findings, with IVUS and OCT providing additional information on the vessel wall structure and intramural hematoma. Non-invasive imaging modalities such as echocardiography, CMR, and CCTA can aid in the assessment and follow-up of SCAD patients, but their diagnostic utility is limited compared to invasive techniques.

6. Management and outcomes of SCAD

The management of SCAD is primarily conservative, as natural healing evolution is observed in many cases (75–77). The majority of SCAD patients are treated conservatively, with no significant difference in MACE between patients with or without percutaneous coronary intervention (PCI) at the index hospitalization (65). Prolonged monitoring in the acute phase is recommended, as some studies have shown that not all conservatively treated patients experience complete healing (2, 76, 77).

The paucity of randomized trials focusing on medical therapy for SCAD has left treatment approaches primarily reliant on empirical strategies. The use of dual antiplatelet therapy (DAPT) in combination with anticoagulant therapy poses a potential risk of hematoma propagation. However, certain studies have documented the presence of intramural thrombus at the site of SCAD (71), providing a rationale for considering DAPT, preferably with a less potent P2Y12 inhibitor, for a duration of

12 months. Conversely, an analysis from the DISCO registry observed a higher incidence rate of adverse cardiovascular outcomes among 132 SCAD patients treated with DAPT (62.9% on aspirin plus clopidogrel, 36.4% on aspirin plus ticagrelor) compared to 67 SCAD patients managed with either aspirin 100 mg or a P2Y12 inhibitor (78). The authors of this study concluded that DAPT might pose a greater risk compared to single antiplatelet therapy for conservatively managed patients. This observation supports the hypothesis that more potent antiplatelet therapy could potentially induce intramural hematoma propagation.

While the use of aspirin therapy lacks a robust foundation in SCAD management, beta-blockers remain a cornerstone in medical treatment to mitigate the potential adverse effects of catecholamine surges. However, these therapeutic regimens are largely empirical and continue to evolve based on individualized approaches. The forthcoming results of the inaugural prospective, randomized, open-label, blinded-endpoint clinical trial, the Beta-blockers and Antiplatelet agents in patients with Spontaneous Coronary Artery Dissection (BA-SCAD), aimed at evaluating the efficacy of pharmacological therapy in SCAD patients, hold the promise of shedding light on this matter (79).

Patients presenting with left ventricular systolic dysfunction should receive treatment in accordance with the latest clinical guidelines. The use of statins in the context of SCAD remains a topic of debate, as some studies have indicated an elevated risk of recurrence, while others have reported lower recurrence rates among individuals using statins (60, 80).

The consideration of PCI in SCAD cases should be judicious, primarily for those experiencing prolonged symptoms and persistent ischemia. In a study conducted by Kotecha et al., a comparative analysis involving 215 SCAD patients who underwent PCI and a matched cohort of SCAD patients managed conservatively was performed (81). The study findings indicated that high-risk SCAD cases [excluding those presenting with STEMI/cardiac arrest, thrombolysis in myocardial infarction (TIMI) 0/1 flow, or proximal dissection] received stents of greater length and exhibited a higher propensity for PCI-related complications. However, it was notable that this subgroup demonstrated more pronounced improvements in coronary flow and exhibited favorable medium-term outcomes concerning major adverse cardiovascular and cerebrovascular events. This assertion is corroborated by the most recent recommendations provided in the guidelines for the management of ACS by the European Society of Cardiology. According to these guidelines, PCI in SCAD is advised solely for patients exhibiting symptomatic manifestations and indicators of ongoing ischemia, coupled with a substantial extent of myocardium at risk and diminished anterograde flow. This recommendation is categorized as Class I, supported by Level of Evidence C (82) Careful techniques, such as balloon angioplasty without stent deployment or the use of specific stent techniques to avoid hematoma propagation, may be employed (53, 83). Surgical revascularization with coronary artery bypass grafting is performed in specific cases, such as PCI failure, left main involvement, or multivessel presentation.

The main concern in the follow-up of SCAD patients is the risk of recurrence. Close monitoring and avoidance of known precipitating factors, such as intense exercise and emotional stress, are recommended. In the case of pregnancy-related SCAD, future pregnancies should be carefully monitored, and non-hormonal contraception methods are recommended. Regular, moderate exercise is proposed for the overall well-being of SCAD patients, despite physical activity being identified as a risk factor for SCAD development.

Overall, further research is needed to better understand the healing process, identify underlying diseases such as fibromuscular dysplasia and connective tissue disorders, and establish optimal management and follow-up protocols for SCAD patients.

7. Future directions and research needs

Future research on SCAD should focus on several key areas to advance our understanding and improve patient outcomes:

1. Pathophysiology and Etiology: Further studies are needed to elucidate the underlying mechanisms and causes of SCAD. This includes investigating the role of hormonal factors, inflammation, genetic predisposition, connective tissue disorders, and autoimmune diseases in the development of SCAD. Identifying specific genetic mutations and molecular pathways associated with SCAD will help in early diagnosis, risk stratification, and targeted therapies.
2. Diagnostic Tools and Algorithms: Developing clear diagnostic algorithms and guidelines for the accurate and timely diagnosis of SCAD is crucial. This involves refining the use of angiography, intravascular imaging techniques (such as IVUS and OCT), non-invasive imaging modalities (such as CMR and CCTA), and genetic testing to differentiate SCAD from other conditions and identify underlying diseases. Standardized criteria for the interpretation of imaging findings and histopathological features of SCAD are needed.
3. Medical Management: Conducting randomized controlled trials to evaluate the efficacy and safety of different medical treatments for SCAD is essential. This includes investigating the optimal duration of DAPT, the role of anticoagulants, the use of beta-blockers and other medications, and the potential benefits of statins in preventing recurrence. Long-term follow-up studies are necessary to assess the outcomes and recurrence rates associated with different treatment strategies.
4. Risk Stratification and Prevention: Developing risk stratification tools to identify patients at higher risk of SCAD recurrence, adverse cardiovascular events, or complications is crucial for personalized management. Understanding the role of lifestyle factors, such as exercise intensity and emotional stress, in triggering SCAD and implementing preventive measures to avoid these triggers is important. Identifying modifiable risk factors and implementing targeted preventive strategies can help reduce the burden of SCAD.

5. Pregnancy and Women's Health: Further research is needed to understand the specific risks and management strategies for pregnancy-related SCAD. This includes investigating the impact of hormonal changes, vascular adaptations during pregnancy, and the use of hormonal therapies and contraceptives on SCAD risk. Developing guidelines and recommendations for family planning and pregnancy management in women with a history of SCAD is necessary.
6. Patient Education and Support: Improving patient awareness, education, and support systems for SCAD are crucial. Providing information on symptoms, risk factors, and preventive measures can help patients recognize early signs and seek appropriate medical attention. Creating patient support networks and resources can enhance patient well-being and improve long-term outcomes.
7. Collaborative efforts between researchers, clinicians, and patient advocacy groups are essential to address these research needs and advance our understanding of SCAD. By conducting high-quality studies and sharing data through registries and international collaborations, we can make significant progress in the diagnosis, management, and prevention of SCAD.

8. Conclusion

In conclusion, SCAD is a unique and complex condition that predominantly affects women, often in their reproductive years. It is characterized by the formation of intramural hematoma, with or without intimal tear, and potential obstruction of blood flow. The recognition and understanding of SCAD have increased in recent years, but many aspects of its pathophysiology, diagnosis, and management remain uncertain.

SCAD is associated with various underlying conditions such as FMD, CTDs, systemic autoimmune diseases, and hormonal changes during pregnancy. Further research is needed to explore the exact mechanisms by which these factors contribute to SCAD development and to develop specific diagnostic algorithms for early and accurate diagnosis.

Management of SCAD primarily involves conservative measures, with a focus on close monitoring and supportive care. While some cases may require invasive interventions such as PCI or coronary artery bypass grafting, the majority of SCAD patients can be managed conservatively. Research is needed to determine the optimal medical therapies and preventive strategies to reduce the risk of recurrence and improve long-term outcomes.

Collaborative efforts between researchers, clinicians, and patient advocacy groups are essential to advance our understanding of SCAD and namely elucidate the exact etiology. Future studies should focus on clarifying the underlying mechanisms, improving diagnostic tools, developing evidence-based treatment approaches, and identifying effective strategies for risk stratification and prevention. By addressing these research needs, we can enhance the management and outcomes of SCAD patients and provide them with appropriate support and care.

9. Limitations

The primary limitation of our review paper is that we did not conduct a systematic review of the literature. Instead, our review took a more focused approach, aiming to synthesize and discuss key concepts and findings within a narrower scope. This might have led to potential omissions of relevant studies that a systematic review would have captured. Furthermore, the absence of a systematic review methodology might impact the overall rigor and comprehensiveness of our review. By not adhering to this methodology, our review paper could be susceptible to selection bias and may not provide a complete and unbiased overview of the literature on the topic. In light of these limitations, we acknowledge that the conclusions drawn in our review should be interpreted with caution. While we aimed to provide valuable insights and perspectives within the chosen scope, the absence of a systematic approach may limit the generalizability and robustness of our findings.

Author contributions

AD: Writing – original draft, Writing – review & editing, Formal Analysis, Funding acquisition, Methodology, Software, Validation. GK: Conceptualization, Formal Analysis, Validation, Writing – review & editing. PM: Formal Analysis, Funding acquisition, Investigation, Supervision, Writing – review & editing. RZ: Data curation, Formal Analysis, Writing – review & editing. VD: Data curation, Formal Analysis, Funding acquisition, Supervision, Writing – review & editing. MM: Software, Writing – review & editing. DP: Software, Writing – review & editing, Data curation, Supervision. BF: Data curation, Supervision, Writing – review & editing, Formal Analysis. SA: Formal Analysis, Supervision, Writing – review & editing, Conceptualization, Funding acquisition, Methodology.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. *Catheter Cardiovasc Interv*. (2014) 84(7):1115–22. doi: 10.1002/ccd.25293

2. Adlam D, Alfonso F, Maas A, Vrints C, Writing Committee. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. 2018;39(36):3353–68. doi: 10.1093/eurheartj/ehy080

3. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. American Heart Association Council on peripheral vascular disease; council on clinical cardiology; council on cardiovascular and stroke nursing; council on genomic and precision medicine; and stroke council. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation*. (2018) 137(19):e523–57. doi: 10.1161/CIR.0000000000000564

4. Saw J, Mancini GBJ, Humphries KH. Contemporary review on spontaneous coronary artery dissection. *J Am Coll Cardiol*. (2016) 68(3):297–312. doi: 10.1016/j.jacc.2016.05.034

5. Lim YT, Ling LH, Tambyah PA, Choo MH. Myocardial infarction in patients aged 40 years and below: an angiographic review. *Singapore Med J*. (1996) 37 (4):352–5.

6. Vautrin E, Jean ABP, Fourny M, Marlière S, Vanzetto G, Bouvaist H, et al. Sex differences in coronary artery lesions and in-hospital outcomes for patients with ST-segment elevation myocardial infarction under the age of 45. *Catheter Cardiovasc Interv*. (2020) 96(6):1222–30. doi: 10.1002/ccd.28627

7. Yang J, Biery DW, Singh A, Divakaran S, DeFilippis EM, Wu WY, et al. Risk factors and outcomes of very young adults who experience myocardial infarction: the partners YOUNG-MI registry. *Am J Med*. (2020) 133(5):605–612.e1. doi: 10.1016/j.amjmed.2019.10.020

8. Elkayam U, Jalnapurkar S, Barakkat MN, Khatri N, Kealey AJ, Mehra A, et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. *Circulation*. (2014) 129 (16):1695–702. doi: 10.1161/CIRCULATIONAHA.113.002054

9. Franke KB, Nerlekar N, Marshall H, Psaltis PJ. Systematic review and meta-analysis of the clinical characteristics and outcomes of spontanous coronary artery dissection. *Int J Cardiol*. (2021) 322:34–9. doi: 10.1016/j.ijcard.2020.08.076

10. Luong C, Starovoytov A, Heydari M, Sedlak T, Aymong E, Saw J. Clinical presentation of patients with spontaneous coronary artery dissection. *Catheter Cardiovasc Interv*. (2017) 89(7):1149–54. doi: 10.1002/ccd.26977

11. Daoulah A, Al-Faifi SM, Madan M, Arafat AA, Hersi AS, Alasmari A, et al. Clinical presentation and outcome of patients with spontaneous coronary artery dissection versus atherosclerotic coronary plaque dissection. *Crit Pathw Cardiol*. (2021) 20(1):36–43. doi: 10.1097/HPC.0000000000000233

12. Loukas M, Groat C, Khangura R, Owens DG, Anderson RH. The normal and abnormal anatomy of the coronary arteries. *Clin Anat*. (2009) 22(1):114–28. doi: 10.1002/ca.20761

13. Spicer DE, Henderson DJ, Chaudhry B, Mohun TJ, Anderson RH. The anatomy and development of normal and abnormal coronary arteries. *Cardiol Young*. (2015) 25 (8):1493–503. doi: 10.1017/S1047951115001390

14. Loukas M, Sharma A, Blaak C, Sorenson E, Mian A. The clinical anatomy of the coronary arteries. *J Cardiovasc Transl Res*. (2013) 6(2):197–207. doi: 10.1007/s12265-013-9452-5

15. Red-Horse K, Ueno H, Weissman IL, Krasnow MA. Coronary arteries form by developmental reprogramming of venous cells. *Nature*. (2010) 464(7288):549–53. doi: 10.1038/nature08873

16. Mulligan-Kehoe MJ, Simons M. Vasa vasorum in normal and diseased arteries. *Circulation*. (2014) 129(24):2557–66. doi: 10.1161/CIRCULATIONAHA.113.007189

17. Houck P. Pathophysiology of spontaneous coronary artery dissection determines anticoagulation strategy. *Cureus*. (2021) 13(8):e17437. doi: 10.7759/cureus.17437

18. Claes E, Atienza JM, Guinea GV, Rojo FJ, Bernal JM, Revuelta JM, et al. Mechanical properties of human coronary arteries. *Annu Int Conf IEEE Eng Med Biol Soc*. (2010) 2010:3792–5. doi: 10.1109/IEMBS.2010.5627560

19. Pretty H. Dissecting aneurysm of coronary artery in a woman aged 42. *Br Med J*. (1931) 1:667.

20. Saw J, Mancini GB, Humphries K, Fung A, Boone R, Starovoytov A, et al. Angiographic appearance of spontaneous coronary artery dissection with intramural hematoma proven on intracoronary imaging. *Catheter Cardiovasc Interv*. (2016) 87 (2):E54–61. doi: 10.1002/ccd.26022

21. Al-Hussaini A, Adlam D. Spontaneous coronary artery dissection. *Heart*. (2017) 103(13):1043–51. doi: 10.1136/heartjnl-2016-310320

22. Tanis W, Stella PR, Kirkels JH, Pijlman AH, Peters RH, de Man FH. Spontaneous coronary artery dissection: current insights and therapy. *Neth Heart J*. (2008) 16(10):344–9. doi: 10.1007/BF03086176

23. Jackson R, Al-Hussaini A, Joseph S, van Soest G, Wood A, Macaya F, et al. Spontaneous coronary artery dissection: pathophysiological insights from optical coherence tomography. *JACC Cardiovasc Imaging*. (2019) 12(12):2475–88. doi: 10.1016/j.jcmg.2019.01.015

24. Tanaka A. Shedding light on pathophysiology of spontaneous coronary artery dissection. *JACC Cardiovasc Imaging*. (2019) 12(12):2489–91. doi: 10.1016/j.jcmg.2019.02.003

25. Kwon TG, Gulati R, Matsuzawa Y, Aoki T, Guddeti RR, Herrmann J, et al. Proliferation of coronary adventitial vasa vasorum in patients with spontaneous coronary artery dissection. *JACC Cardiovasc Imaging*. (2016) 9(7):891–2. doi: 10.1016/j.jcmg.2015.11.030

26. Mandal R, Brooks EG, Corliss RF. Eosinophilic coronary periarteritis with arterial dissection: the mast cell hypothesis. *J Forensic Sci*. (2015) 60(4):1088–92. doi: 10.1111/1556-4029.12752

27. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, et al. Canadian Spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J*. (2019) 40(15):1188–97. doi: 10.1093/eurheartj/ehz007

28. Robinowitz M, Virmani R, JrU MH. Spontaneous coronary artery dissection and eosinophilic inflammation: a cause and effect relationship? *Am J Med*. (1982) 72 (6):923–8. doi: 10.1016/0002-9343(82)90853-1.)

29. Canga Y, Guvenc TS, Calik AN, Karatas MB, Bezgin T, Onuk T, et al. Systemic inflammatory activation in patients with acute coronary syndrome secondary to nonatherosclerotic spontaneous coronary artery dissection. *North Clin Istanb*. (2018) 5(3):186–94. doi: 10.14744/nci.2017.59244.)

30. Wolny RR, Kwieciński J, Zalewska J, Michałowska I, Kruk M, Kepka C, et al. Pericoronary adipose tissue density is increased in patients with recent spontaneous coronary dissection. *Heart*. (2023) 109(19):1443–9. doi: 10.1136/heartjnl-2023-322482

31. Margaritis M, Saini F, Baranowska-Clarke AA, Parsons S, Vink A, Budgeon C, et al. Vascular histopathology and connective tissue ultrastructure in spontaneous coronary artery dissection: pathophysiological and clinical implications. *Cardiovasc Res*. (2022) 118(7):1835–48. doi: 10.1093/cvr/cvab183

32. Carss KJ, Baranowska AA, Armisen J, Webb TR, Hamby SE, Premawardhana D, et al. Spontaneous coronary artery dissection: insights on rare genetic variation from genome sequencing. *Circ Genom Precis Med*. (2020) 13:e003030. doi: 10.1161/CIRCGEN.120.003030

33. Adlam D, Olson TM, Combaret N, Kovacic JC, Iismaa SE, Al-Hussaini A, et al. DISCO Consortium; CARDIoGRAMPlusC4D study group. Association of the PHACTR1/EDN1 genetic locus with spontaneous coronary artery dissection. *J Am Coll Cardiol*. (2019) 73:58–66. doi: 10.1016/j.jacc.2018.09.085

34. Adlam D, Berrandou TE, Georges A, Nelson CP, Giannoulatou E, Henry J, et al. Genome-wide association meta-analysis of spontaneous coronary artery dissection identifies risk variants and genes related to artery integrity and tissue-mediated coagulation. *Nat Genet*. (2023) 55(6):964–72. doi: 10.1038/s41588-023-01410-1

35. Nebeski D, Basic C, Svanvik T, Schaufelberger M, Ostgard Thunstrom E, SWEDPREG. Incidence of spontaneous coronary artery dissection during pregnancy in Swedish women between 1997 and 2019, a retrospective observational cohort study based on national Swedish health-registers. *Eur. Heart J*. 2022; 43 (2): ehac544-1172. doi: 10.1093/eurheartj/ehac544.1172 ehac544-1172

36. Ghossein-Doha C, Khalil A, Lees CC. Maternal hemodynamics: a 2017 update. *Ultrasound Obstet Gynecol*. (2017) 49(1):10–4. doi: 10.1002/uog.17377

37. Cano-Castellote M, Afanador-Restrepo DF, González-Santamaría J, Rodríguez-López C, Castellote-Caballero Y, Hita-Contreras F, et al. Pathophysiology, diagnosis and treatment of spontaneous coronary artery dissection in peripartum women. *J Clin Med*. (2022) 11(22):6657. doi: 10.3390/jcm11226657

38. Osol G, Ko NL, Mandalà M. Plasticity of the maternal vasculature during pregnancy. *Annu Rev Physiol*. (2019) 81:89–111. doi: 10.1146/annurev-physiol-020518-114435

39. Almeda FQ, Barkatullah S, Kavinsky CJ. Spontaneous coronary artery dissection. *Clin Cardiol*. (2004) 27(7):377–80. doi: 10.1002/clc.4960270702.

40. Kamineni R, Sadhu A, Alpert JS. Spontaneous coronary artery dissection: report of two cases and a 50-year review of the literature. *Cardiol Rev*. (2002) 10(5):279–84. doi: 10.1097/00045415-200209000-00004

41. European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al., ESC Committee for practice guidelines. ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European society of cardiology (ESC). *Eur Heart J*. 2011;32(24):3147–97. doi: 10.1093/eurheartj/ehr218

42. Vijayaraghavan R, Verma S, Gupta N, Saw J. Pregnancy-related spontaneous coronary artery dissection. *Circulation*. (2014) 130(21):1915–20. doi: 10.1161/CIRCULATIONAHA.114.011422

43. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best PJM. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol*. (2017) 70 (4):426–35. doi: 10.1016/j.jacc.2017.05.055

44. Tweet MS, Young KA, Best PJM, Hyun M, Gulati R, Rose CH, et al. Association of pregnancy with recurrence of spontaneous coronary artery dissection among women with prior coronary artery dissection. *JAMA Netw Open*. (2020) 3(9): e2018170. doi: 10.1001/jamanetworkopen.2020.18170

45. Chi G, Najafi H, Montazerin SM, Lee JJ. Factors associated with recurrent spontaneous coronary artery dissection: a systematic review and meta-analysis. *Coron Artery Dis*. (2022) 33(7):566–73. doi: 10.1097/MCA.0000000000001168

46. Edupuganti MM, Ganga V. Acute myocardial infarction in pregnancy: current diagnosis and management approaches. *Indian Heart J*. (2019) 71(5):367–74. doi: 10.1016/j.ihj.2019.12.003

47. Zehir R, Karabay CY, Kocabay G. Myocardial infarction and spontaneous dissection of coronary artery due to oral contraceptive. *J Cardiovasc Med (Hagerstown)*. (2011) 12(6):448–50. doi: 10.2459/JCM.0b013e3283467fc9

48. Saw J, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv*. (2014) 7(5):645–55. doi: 10.1161/CIRCINTERVENTIONS.114.001760

49. Slight R, Behranwala AA, Nzewi O, Sivaprakasam R, Brackenbury E, Mankad P. Spontaneous coronary artery dissection: a report of two cases occurring during menstruation. *N Z Med J*. (2003) 116(1181):U585.

50. Díez-Villanueva P, García-Guimaraes MM, Macaya F, Masotti M, Nogales JM, Jimenez-Kockar M, et al. Spontaneous coronary artery dissection and menopause. *Am J Cardiol*. (2021) 148:53–9. doi: 10.1016/j.amjcard.2021.02.007

51. Camacho Freire SJ, Díaz Fernández JF, Gheorghe LL, Gómez Menchero AE, León Jiménez J, Roa Garrido J, et al. Spontaneous coronary artery dissection and hypothyroidism. *Rev Esp Cardiol (Engl Ed)*. (2019) 72(8):625–33. doi: 10.1016/j.rec.2018.06.031

52. Henkin S, Negrotto SM, Tweet MS, Kirmani S, Deyle DR, Gulati R, et al. Spontaneous coronary artery dissection and its association with heritable connective tissue disorders. *Heart*. (2016) 102(11):876–81. doi: 10.1136/heartjnl-2015-308645

53. Lewey J, El Hajj SC, Hayes SN. Spontaneous coronary artery dissection: new insights into this not-so-rare condition. *Annu Rev Med*. (2022) 73:339–54. doi: 10.1146/annurev-med-052819-023826

54. Murphy-Ryan M, Psychogios A, Lindor NM. Hereditary disorders of connective tissue: a guide to the emerging differential diagnosis. *Genet Med*. (2010) 12(6):344–54. doi: 10.1097/GIM.0b013e3181e074f0

55. Bax M, Romanov V, Junday K, Giannoulatou E, Martinac B, Kovacic JC, et al. Arterial dissections: common features and new perspectives. *Front Cardiovasc Med*. (2022) 9:1055862. doi: 10.3389/fcvm.2022.1055862

56. Boutari C, Georgianou E, Sachinidis A, Katsimardou A, Christou K, Piperidou A, et al. Renovascular hypertension: novel insights. *Curr Hypertens Rev*. (2020) 16 (1):24–9. doi: 10.2174/1573402115666190416153321

57. Plouin PF, Perdu J, La Batide-Alanore A, Boutouyrie P, Gimenez-Roqueplo AP, Jeunemaitre X. Fibromuscular dysplasia. *Orphanet J Rare Dis*. (2007) 2:28. doi: 10.1186/1750-1172-2-28

58. Pate GE, Lowe R, Buller CE. Fibromuscular dysplasia of the coronary and renal arteries? *Catheter Cardiovasc Interv*. (2005) 64(2):138–45. doi: 10.1002/ccd.20246

59. Saw J, Poulter R, Fung A, Wood D, Hamburger J, Buller CE. Spontaneous coronary artery dissection in patients with fibromuscular dysplasia: a case series. *Circ Cardiovasc Interv*. (2012) 5(1):134–7. doi: 10.1161/CIRCINTERVENTIONS

60. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation*. (2012) 126(5):579–88. doi: 10.1161/CIRCULATIONAHA.112.105718

61. Persu A, Lopez-Sublet M, Al-Hussaini A, Pappaccogli M, Radhouani I, Van der Niepen P, et al. Prevalence and disease spectrum of extracoronary arterial abnormalities in spontaneous coronary artery dissection. *JAMA Cardiol*. (2022) 7 (2):159–66. doi: 10.1001/jamacardio.2021.4690

62. Ullah W, Ali Z, Khanal S, Khan M, Gajanan G, Sattar Y, et al. Spontaneous coronary artery dissection secondary to rheumatological diseases: a comprehensive review. *Cureus*. (2019) 11(7):e5231. doi: 10.7759/cureus.5231

63. Kronzer VL, Tarabochia AD, Lobo Romero AS, Tan NY, O'Byrne TJ, Crowson CS, et al. Lack of association of spontaneous coronary artery dissection with autoimmune disease. *J Am Coll Cardiol*. (2020) 76(19):2226–34. doi: 10.1016/j.jacc.2020.09.533

64. Civieri G, Vadori M, Masiero G, Iop L, Tansella D, Pergola V, et al. Spontaneous coronary artery dissection in women with acute myocardial infarction: is there a new role for autoimmunity? *Eur Heart J Acute Cardiovasc Care*. (2023):zuad070. doi: 10.1093/ehjacc/zuad070. [Epub ahead of print]

65. Tweet MS, Eleid MF, Best PJ, Lennon RJ, Lerman A, Rihal CS, et al. Spontaneous coronary artery dissection: revascularization versus conservative therapy. *Circ Cardiovasc Interv*. (2014) 7(6):777–86. doi: 10.1161/CIRCINTERVENTIONS.114.001659

66. Lettieri C, Zavalloni D, Rossini R, Morici N, Ettori F, Leonzi O, et al. Management and long-term prognosis of spontaneous coronary artery dissection. *Am J Cardiol*. (2015) 116(1):66–73. doi: 10.1016/j.amjcard.2015.03.039

67. Eleid MF, Guddeti RR, Tweet MS, Lerman A, Singh M, Best PJ, et al. Coronary artery tortuosity in spontaneous coronary artery dissection: angiographic characteristics and clinical implications. *Circ Cardiovasc Interv*. (2014) 7(5):656–62. doi: 10.1161/CIRCINTERVENTIONS.114.001676

68. Saw J. Spontaneous coronary artery dissection. *Can J Cardiol*. (2013) 29 (9):1027–33. doi: 10.1016/j.cjca.2012.12.018

69. Alfonso F, Bastante T, García-Guimaraes M, Pozo E, Cuesta J, Rivero F, et al. Spontaneous coronary artery dissection: new insights into diagnosis and treatment. *Coron Artery Dis*. (2016) 27(8):696–706. doi: 10.1097/MCA.0000000000000412

70. Maehara A, Mintz GS, Castagna MT, Pichard AD, Satler LF, Waksman R, et al. Intravascular ultrasound assessment of spontaneous coronary artery dissection. *Am J Cardiol*. (2002) 89(4):466–8. doi: 10.1016/s0002-9149(01)02272-x

71. Alfonso F, Paulo M, Gonzalo N, Dutary J, Jimenez-Quevedo P, Lennie V, et al. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. *J Am Coll Cardiol*. (2012) 59(12):1073–9. doi: 10.1016/j.jacc.2011.08.082

72. Barbieri L, D'Errico A, Avallone C, Gentile D, Provenzale G, Guagliumi G, et al. Optical coherence tomography and coronary dissection: precious tool or useless surplus? *Front Cardiovasc Med*. (2022) 9:822998. doi: 10.3389/fcvm.2022.822998

73. Tan NY, Hayes SN, Young PM, Gulati R, Tweet MS. Usefulness of cardiac magnetic resonance imaging in patients with acute spontaneous coronary artery dissection. *Am J Cardiol*. (2018) 122(10):1624–9. doi: 10.1016/j.amjcard.2018.07.043

74. Marrazzo G, Palermi S, Pastore F, Ragni M, De Luca M, Gambardella M, et al. Multimodality imaging approach to spontaneous coronary artery dissection. *J Clin Med*. (2022) 12(1):154. doi: 10.3390/jcm12010154

75. Saw J, Starovoytov A, Aymong E, Inohara T, Alfadhel M, McAlister C, et al. Canadian spontaneous coronary artery dissection cohort study: 3-year outcomes. *J Am Coll Cardiol*. (2022) 80(17):1585–97. doi: 10.1016/j.jacc.2022.08.759

76. Nakashima T, Noguchi T, Haruta S, Yamamoto Y, Oshima S, Nakao K, et al. Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: a report from the angina pectoris-myocardial infarction multicenter investigators in Japan. *Int J Cardiol*. (2016) 207:341–8. doi: 10.1016/j.ijcard.2016.01.188

77. McGrath-Cadell L, McKenzie P, Emmanuel S, Muller DW, Graham RM, Holloway CJ. Outcomes of patients with spontaneous coronary artery dissection. *Open Heart*. (2016) 3(2):e000491. doi: 10.1136/openhrt-2016-000491

78. Cerrato E, Giacobbe F, Quadri G, Macaya F, Bianco M, Mori R, et al.; DISCO collaborators. Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry. *Eur Heart J*. (2021) 42(33):3161–71. doi: 10.1093/eurheartj/ehab372

79. Alfonso F, de la Torre Hernández JM, Ibáñez B, Sabaté M, Pan M, Gulati R, et al. Rationale and design of the BA-SCAD (Beta-blockers and antiplatelet agents in patients with spontaneous coronary artery dissection) randomized clinical trial. *Rev Esp Cardiol (Engl Ed)*. 2022;75(6):515–22. English, Spanish. doi: 10.1016/j.rec.2021.08.003

80. Feldbaum E, Thompson EW, Cook TS, Sanghavi M, Wilensky RL, Fiorilli PN, et al. Management of spontaneous coronary artery dissection: trends over time. *Vasc Med*. (2023) 28(2):131–8. doi: 10.1177/1358863X231155305

81. Kotecha D, Garcia-Guimaraes M, Premawardhana D, Pellegrini D, Oliver-Williams C, Bountziouka V, et al. Risks and benefits of percutaneous coronary intervention in spontaneous coronary artery dissection. *Heart*. (2021) 107 (17):1398–406. doi: 10.1136/heartjnl-2020-318914

82. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. ESC Scientific document group. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J*. (2023) 44(38):3720–826. doi: 10.1093/eurheartj/ehad191

83. Motreff P, Barber-Chamoux N, Combaret N, Souteyrand G. Coronary artery fenestration guided by optical coherence tomography before stenting: new interventional option in rescue management of compressive spontaneous intramural hematoma. *Circ Cardiovasc Interv*. (2015) 8(4):e002266. doi: 10.1161/CIRCINTERVENTIONS.114.002266

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 09 November 2023
DOI 10.3389/fcvm.2023.1270530

OPEN ACCESS

EDITED BY
Alessio Mattesini,
Careggi University Hospital, Italy

REVIEWED BY
Enrico Marchi,
University of Florence, Italy
Daniel Cesarini,
Careggi University Hospital, Italy

*CORRESPONDENCE
Bojan Maričić
bokimaricic@gmail.com
Mihajlo Bojanović
drmihajloboj@gmail.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 31 July 2023
ACCEPTED 16 October 2023
PUBLISHED 09 November 2023

CITATION
Maričić B, Perišić Z, Kostić T, Božinović N, Petrović M, Čanković M, Mehmedbegović Z, Juričić S, Vasilev V, Dakić S, Perišić J, Milošević J, Bojanović M, Nikolić M, Maričić T and Apostolović S (2023) An analysis of published cases of cutting balloon use in spontaneous coronary artery dissection. Front. Cardiovasc. Med. 10:1270530. doi: 10.3389/fcvm.2023.1270530

An analysis of published cases of cutting balloon use in spontaneous coronary artery dissection

Bojan Maričić[1*†], Zoran Perišić[1,2†], Tomislav Kostić[1,2†], Nenad Božinović[1,2], Milovan Petrović[3,4], Milenko Čanković[3,4], Zlatko Mehmedbegović[5,6], Stefan Juričić[5], Vladimir Vasilev[7], Sonja Dakić[1,2], Jelena Perišić[1], Jelena Milošević[1], Mihajlo Bojanović[1*], Miroslav Nikolić[1], Tijana Maričić[8] and Svetlana Apostolović[1,2]

[1]Department of Cardiology, University Clinical Center Nis, Niš, Serbia, [2]Faculty of Medicine, Department of Internal Medicine, University of Nis, Niš, Serbia, [3]Department of Cardiology, Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia, [4]Faculty of Medicine, Department of Internal Medicine, University of Novi Sad, Novi Sad, Serbia, [5]Department of Cardiology, University Clinical Center Belgrade, Belgrade, Serbia, [6]Faculty of Medicine, Department of Internal Medicine, University of Belgrade, Belgrade, Serbia, [7]Department of Cardiology, VFV Clinic Skopje, Skopje, North Macedonia, [8]Department of Anesthesiology, Resuscitation and Intensive Therapy, University Clinical Center Nis, Niš, Serbia

Introduction: SCAD involves a sudden tear or separation within the layers of the coronary artery wall, resulting in blood flow obstruction and subsequent myocardial ischemia.
Materials and methods: A comprehensive literature search was conducted to identify relevant published cases of cutting balloon use in patients diagnosed with spontaneous coronary artery dissection. Electronic databases including PubMed, MEDLINE, Embase, Cochrane Library and Google Scholar were systematically searched from inception until the present using terms "cutting balloon," "SCAD," "acute coronary syndrome," "intramural hematoma," and "angioplasty."
Results: A total of 32 published cases of cutting balloon use in spontaneous coronary artery dissection were analyzed in this study. The majority of the patients included in the analysis were female without prior history of cardiovascular disease. The median age of the SCAD population was approximately 46 years. The most frequently affected artery in SCAD cases was the Left Anterior Descending artery. Intravascular ultrasound was utilized more frequently than other modalities of adjunctive imaging techniques. The most frequent complication was the distal propagation of hematoma. Despite the successful dilation achieved with the cutting balloon, in some cases stenting was required to provide additional support.
Conclusion: The results of this analysis demonstrate that cutting balloon use in SCAD cases yields favorable outcomes.

KEYWORDS

cutting balloon, spontaneous coronary artery dissection, acute coronary syndrome, angioplasty, intramural hematoma

1. Introduction

Spontaneous coronary artery dissection (SCAD) is a rare but increasingly recognized cause of acute coronary syndrome, particularly in young women without traditional cardiovascular risk factors. SCAD involves a sudden tear or separation within the layers of the coronary artery wall, resulting in intramural hematoma formation, blood flow obstruction and subsequent myocardial ischemia (**Supplementary Figure 1**) (1).

SCAD can be classified based on angiographic findings as (2):

- Type 1 (an obvious stain on the wall of the artery with the presence of a double lumen)
- Type 2 (diffuse smooth stenosis of varying degrees, usually >20–30 mm)
- Type 3 (focal or tubular stenosis mimicking atherosclerosis usually 11–20 mm)
- Type 4 (dissection leading to a sudden total occlusion, usually of the distal coronary segment)

Among the evolving treatment modalities, the utilization of cutting balloons has garnered significant attention as a potential intervention in SCAD cases. Cutting balloons, initially designed for angioplasty procedures, employ microsurgical blades mounted on the surface of a balloon to incise and dilate the affected arterial segment. This unique mechanism offers potential benefits in dissection management by creating controlled micro-incisions within the affected vessel, causing intimal fenestration and hematoma draining (**Supplementary Figure 2**) (3, 4).

While the use of cutting balloons in SCAD treatment has gained some clinical traction, the body of evidence supporting its efficacy and safety remains limited. Published cases reporting the application of cutting balloons in SCAD cases offer valuable insights into the procedural aspects, outcomes, and potential benefits or drawbacks associated with this approach (5, 6).

Therefore, this paper aims to perform a comprehensive analysis of published cases of cutting balloon use in SCAD. By synthesizing existing data, we intend to evaluate the clinical outcomes, technical considerations, and potential complications associated with the utilization of cutting balloons in this unique patient population.

The findings from this analysis have the potential to enhance our understanding of the role of cutting balloons in SCAD management and guide clinical decision-making in treating this challenging condition. As SCAD remains an underdiagnosed and understudied entity, this paper aims to contribute to the growing body of literature on novel therapeutic strategies, further advancing the field and ultimately improving patient outcomes.

2. Materials and methods

A comprehensive literature search was conducted to identify relevant published cases of cutting balloon use in patients diagnosed with SCAD. Electronic databases including PubMed, Embase, and Cochrane Library were systematically searched from inception until the present, with no language restrictions. The search strategy involved a combination of controlled vocabulary terms (MeSH terms) and keywords related to "cutting balloon," "SCAD," "acute coronary syndrome," "intramural hematoma," and "angioplasty." Additionally, reference lists of included studies and relevant review articles were manually screened for additional eligible cases.

The extracted data were tabulated and qualitatively analyzed to identify patterns, trends, and potential associations. Descriptive statistics, including frequencies and percentages, were used to summarize categorical variables, while continuous variables were reported as means or medians with corresponding measures of variability.

3. Results

A total of 32 published cases of cutting balloon use in SCAD were analyzed in this study (7–32). The majority of the patients included in the analysis were female ($n = 30$, 93.75% female, $n = 2$, 6.25% male) and had no prior history of cardiovascular disease (CVD). The median age of the SCAD population was approximately 46 years (28–73 years). The most frequently affected artery in SCAD cases was the Left Anterior Descending (LAD) artery, observed in $n = 24$, 75% of the cases.

Overall, the procedural outcomes of cutting balloon use in SCAD were encouraging. The majority of cases resulted in a Thrombolysis In Myocardial Infarction (TIMI) 3 flow restoration ($n = 30$, 93.75% of cases) (**Supplementary Table 1**). This indicates successful reperfusion and optimal blood flow through the affected coronary artery.

In terms of adjunctive imaging techniques, intravascular ultrasound (IVUS) was utilized more frequently than other modalities. IVUS was employed in $n = 53.12\%$ of the cases, providing detailed information about the extent and characteristics of the dissection and helping guide the cutting balloon intervention.

In some cases, additional treatment was necessary after cutting balloon angioplasty. Stenting was performed as a follow-up intervention in $n = 12$, 37.5% of the cases (**Supplementary Table 1**). This suggests that despite the successful dilation achieved with the cutting balloon, stenting may be the final option to provide additional support and stabilize the dissected coronary artery.

It is worth noting that the specific outcomes related to procedural success, TIMI flow, and the need for additional interventions may vary depending on individual patient characteristics, severity of SCAD, and the expertise of the operators.

The diameter of the cutting balloons used in the analyzed cases was consistently smaller than the vessel diameter, with the most common size being 2.5 mm ($n = 11$, 35.49%) (**Supplementary Table 1**). This approach of using a smaller cutting balloon size compared to the vessel diameter aimed to minimize the risk of

vessel injury and optimize the efficacy of the procedure (**Supplementary Figure 2**).

Among the reported complications, the most frequently encountered was the distal propagation of the subintimal hematoma. This complication occurred in $n = 6$, 18.75% of the cases and highlights the importance of careful monitoring and management during and after CB angioplasty and stenting.

The deployment of the cutting balloon was primarily carried out at the level of the maximal lumen compression (**Supplementary Figure 2**). If there was no visual improvement, distal inflations were done. This approach allowed for precise positioning of the cutting balloon and focused dilatation within the affected segment. By targeting the lesion directly, the cutting balloon intervention aimed to effectively modify the dissected arterial segment while minimizing unnecessary trauma to the surrounding healthy tissue.

Furthermore, the majority of patients included in the analysis presented with ST-elevation myocardial infarction (STEMI) $n = 10$, 31.25%. This suggests that SCAD, particularly when involving the LAD artery, can lead to severe ischemic events requiring urgent intervention. The utilization of cutting balloons in these STEMI patients aimed to promptly restore blood flow and salvage viable myocardium.

Overall, the results of this analysis demonstrate that cutting balloon use in SCAD cases, particularly among female patients with no prior history of CVD, yields favorable outcomes. However, further research is warranted to explore the long-term clinical implications, patient prognosis, and compare the effectiveness of cutting balloon angioplasty to other treatment approaches in SCAD management.

4. Discussion

The management of SCAD remains a challenging clinical scenario due to its unpredictable presentation and potential for catastrophic outcomes. In recent years, cutting balloons have emerged as a potential therapeutic option for SCAD, offering a unique approach to dissection management.

Our analysis revealed several key findings that contribute to the existing knowledge base on the role of cutting balloons in SCAD management. Firstly, we observed that stenting was employed as an adjunctive therapy rather than a standalone treatment modality (**Supplementary Table 1**) (8, 13, 15, 16, 18, 20, 27, 28, 29, 31, 32). In all of the cases where stenting was performed, it was utilized in combination with cutting balloon angioplasty. This suggests that cutting balloons may serve as a useful tool in the armamentarium of SCAD treatment, augmenting the effects of conventional therapies.

Although majority of cases did not have a previous history of cardiovascular diseases $n = 7$, 21,87%, some cases described SCAD during pregnancy or early postpartum, which can be consider as provoking state. [Macaya, Matsuura, Mailey, Somerville, Ejima, Low]. Hormonal and hemodynamic changes during pregnancy can provoke SCAD. Increase in sympathetic activity and activation of the renin-angiotensin-aldosterone system with increased cardiac output, blood volume and red cell mass are considered to cause weakness of aortic wall, which can further propagate to coronary arteries (33, 34). High estrogene and progesterone level during pregnancy through decomposition exovascular structural support also may contribute to SCAD (33, 35).

Regarding clinical outcomes, our analysis showed that cutting balloon use in SCAD was associated with a high rate of technical success, as evidenced by satisfactory angiographic results and resolution of coronary flow abnormalities (**Supplementary Table 1**). The controlled micro-incisions created by cutting balloons seemed to decompress the true lumen and restore adequate blood flow. This may be particularly beneficial in cases of localized dissections or focal stenoses. Moreover, the reported TIMI 3 flow restoration observed in 87.5% of cases supports the potential functional benefits of cutting balloon angioplasty in SCAD patients.

While cutting balloon use demonstrated promising results, it is crucial to acknowledge the potential complications associated with this technique. Our analysis revealed a low incidence of major adverse events, such as coronary perforation, dissection extension, or acute vessel closure. However, it is important to note that in 84.37% of published cases reported a relatively short-term follow-up, limiting our understanding of the long-term outcomes and potential late complications associated with cutting balloon use. Therefore, the safety profile of cutting balloon angioplasty in SCAD warrants further investigation with larger prospective studies and longer-term follow-up.

Furthermore, it is worth highlighting that the existing evidence on cutting balloon use in SCAD is predominantly derived from case reports and small case series, resulting in inherent limitations. The lack of standardized reporting, heterogeneity in procedural techniques, and potential publication bias may limit the generalizability of our findings. Additionally, the absence of a comparative group receiving conventional treatment modalities, such as medical therapy or percutaneous coronary intervention (PCI), hinders our ability to draw definitive conclusions regarding the superiority or inferiority of cutting balloon use in SCAD management.

Despite these limitations, our analysis provides valuable insights into the use of cutting balloons in SCAD and highlights the need for further research in this area. Future studies should focus on larger-scale prospective investigations comparing cutting balloon angioplasty with standard treatment approaches to establish its role in the overall management algorithm for SCAD. Long-term follow-up and comprehensive evaluation of functional outcomes, including exercise capacity and quality of life measures, would help assess the durability of the benefits associated with cutting balloon use.

Conventional PCI for SCAD on the other hand highlights a high periprocedural failure rate and a significant increase in Major Adverse Cardiovascular Events (MACE). The results indicate that PCI was successful in only 34.7% of cases, partially successful in 37.3%, and outright unsuccessful in 28.0%. The propagation of SCAD occurred in 44.0% of cases, and residual dissection was observed in 58.6% of cases. This substantial rate of PCI failures suggests that the conventional approach may not be suitable for a considerable proportion of SCAD patients (36).

Antiplatelet therapy is a fundamental component of drug therapy in SCAD, with 92.3% of patients who underwent CB angioplasty receiving some form of such treatment. Because of the nature of CB employment and subsequent controlled coronary vessel wall damage, antiplatelet therapy is used to prevent platelet aggregation and thrombus formation within the dissected coronary artery. While the use of antiplatelet therapy is widespread in SCAD management, several important considerations deserve attention.

SCAD is a heterogeneous condition, and the choice of antiplatelet therapy should be tailored to each patient's specific presentation. Some SCAD patients may have underlying connective tissue disorders, making them more prone to bleeding complications, while others may require more aggressive platelet inhibition. The use of dual antiplatelet therapy, typically combining aspirin and clopidogrel, was used in 66.66% of patients that received antiplatelet therapy. This approach aims to provide more potent platelet inhibition. However, while it is mandatory for patients who received a stent, it raises concerns about bleeding risk and healing difficulty, particularly in patients who underwent CB angioplasty without stenting. The use of ASA alone was reported in only two cases (17, 30) while and additional two had a relatively short DAPT time of 3 months followed by ASA therapy alone (21). Determining the optimal duration of antiplatelet therapy in SCAD patients remains a challenge. While some patients may benefit from long-term therapy to prevent recurrence, others may face an increased risk of bleeding complications with extended treatment. Clinicians must balance the need for ongoing protection against the risk of adverse events. Regular monitoring of patients on antiplatelet therapy is essential. Platelet function tests, bleeding risk assessments, and coronary imaging may help guide treatment decisions. Close follow-up allows clinicians to adjust therapy based on the patient's response and evolving clinical circumstances.

In addition to the information provided earlier, it's crucial to acknowledge the limited data available regarding the specific type of drug therapy used in SCAD patients. Out of the published cases, only 40.62% reported details about the specific drugs employed in their treatment. This lack of comprehensive data highlights a need for more standardized reporting in SCAD research and a greater emphasis on documenting the types of drug therapies administered.

5. Conclusion

In the case of distal, non-occlusive lesions without ongoing ischemia, the consensus is that they should be treated conservatively with prolonged outpatient follow up.

There is still no consensus on optimal treatment when it comes to occlusive proximal lesions with ongoing ischemia, because conventional stenting usually does not provide adequate results (hematoma and dissection propagation.

In conclusion, our analysis of published cases of cutting balloon use in SCAD demonstrates the potential of this intervention in the management of this complex condition. Cutting balloon angioplasty appears to be a technically feasible and safe adjunctive therapy, offering favorable angiographic outcomes and symptomatic relief. However, the limitations inherent in the available evidence necessitate further research to establish the role of cutting balloons in SCAD and optimize patient outcomes.

Data availability statement

The datasets analysed for this study can be found in PubMed, Embase, and Cochrane Library [https://pubmed.ncbi.nlm.nih.gov, https://www.embase.com/landing?status = grey, https://www.cochranelibrary.com].

Author contributions

BM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. TK: Conceptualization, Project administration, Resources, Writing – original draft. ZP: Conceptualization, Project administration, Resources, Writing – original draft. NB: Formal Analysis, Investigation, Supervision, Writing – review & editing. MP: Formal Analysis, Supervision, Writing – review & editing. MC: Formal Analysis, Supervision, Writing – review & editing. ZM: Data curation, Formal Analysis, Methodology, Writing – review & editing. SJ: Data curation, Formal Analysis, Methodology, Writing – review & editing. VV: Data curation, Formal Analysis, Methodology, Writing – review & editing. SD: Data curation, Investigation, Writing – review & editing. JP: Data curation, Investigation, Writing – review & editing. JM: Formal Analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. MB: Data curation, Investigation, Writing – original draft, Writing – review & editing. MN: Data curation, Formal analysis, Investigation, Writing – review & editing. TM: Data curation, Investigation, Writing – review & editing. SA: Formal Analysis, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of

their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1270530/full#supplementary-material

References

1. Hayes SN, Tweet MS, Adlam D, Kim ES, Gulati R, Price JE, et al. Spontaneous coronary artery dissection: JACC state-of-the-art review. *J Am Coll Cardiol*. (2020) 76(8):961–84. doi: 10.1016/j.jacc.2020.05.084

2. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. *Catheter Cardiovasc Interv*. (2014) 84(7):1115–22. doi: 10.1002/ccd.25293

3. Yumoto K, Sasaki H, Aoki H, Kato K. Successful treatment of spontaneous coronary artery dissection with cutting balloon angioplasty as evaluated with optical coherence tomography. *JACC Cardiovasc Interv*. (2014) 7(7):817–9. doi: 10.1016/j.jcin.2013.10.027

4. Motreff P, Barber-Chamoux N, Combaret N, Souteyrand G. Coronary artery fenestration guided by optical coherence tomograhy before stenting: new interventional option in rescue management of compressive spontaneous intramural hematoma. *Circ Cardiovasc Interv*. (2015) 8(4):e002266. doi: 10.1161/CIRCINTERVENTIONS.114.002266

5. Alfonso F, Paulo M, Lennie V, Dutary J, Bernardo E, Jiménez-Quevedo P, et al. Spontaneous coronary artery dissection: long-term follow-up of a large series of patients prospectively managed with a "conservative" therapeutic strategy. *JACC Cardiovasc Interv*. (2012) 5(10):1062–70. doi: 10.1016/j.jcin.2012.06.014

6. Hayes SN, Kim ES, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American heart association. *Circulation*. (2018) 137(19): e523–57. doi: 10.1161/CIR.0000000000000564

7. Main A, Lombardi WL, Saw J. Cutting balloon angioplasty for treatment of spontaneous coronary artery dissection: case report, literature review, and recommended technical approaches. *Cardiovasc Diagn Ther*. (2019) 9(1):50. doi: 10.21037/cdt.2018.10.11

8. McGrath BM, Vo MN. Novel use of cutting balloon to manage compressive subintimal hematoma during left main stenting in a patient with spontaneous coronary artery dissection. *Clin Case Rep*. (2018) 6(7):1291. doi: 10.1002/ccr3.1531

9. Zghouzi M, Pacha HM, Sattar Y, Alraies MC. Successful treatment of spontaneous coronary artery dissection with cutting balloon angioplasty. *Cureus*. (2021) 13(3):1–4. doi: 10.7759/cureus.13706.

10. Sharma H, Vetrugno V, Khan SQ. Successful treatment of a spontaneous right coronary artery dissection with a 4-mm diameter cutting balloon: a case report. *Eur Heart J Case Rep*. (2019) 3(4):1. doi: 10.1093/ehjcr/ytz212

11. Kaya E, Iwata H, Miyazaki S, Mattson PC, Takamura K, Nishiyama H, et al. Successful coronary flow restoration by stent-free strategy using the pull-back method of cutting balloon in spontaneous coronary artery dissection. *CJC Open*. (2019) 1(4):213–5. doi: 10.1016/j.cjco.2019.05.008

12. Matsuura S, Otowa K, Maruyama M, Usuda K. Successful revascularization with percutaneous coronary intervention using a combination of the subintimal transcatheter withdrawal technique and coronary artery fenestration for spontaneous coronary artery dissection. *Clin Case Rep*. (2021) 9(11):e05045. doi: 10.1002/ccr3.5045

13. Alkhouli M, Cole M, Ling FS. Coronary artery fenestration prior to stenting in spontaneous coronary artery dissection. *Catheter Cardiovasc Interv*. (2016) 88(1): E23–7. doi: 10.1002/ccd.26161

14. Ito T, Shintani Y, Ichihashi T, Fujita H, Ohte N. Non-atherosclerotic spontaneous coronary artery dissection revascularized by intravascular ultrasonography-guided fenestration with cutting balloon angioplasty. *Cardiovasc Interv Ther*. (2017) 32:241–3. doi: 10.1007/s12928-016-0397-x

15. Bresson D, Calcaianu M, Lawson B, Jacquemin L. Coronary artery fenestration as rescue management of intramural haematoma with luminal compression. *Catheter Cardiovasc Interv*. (2019) 94(1):E17–9. doi: 10.1002/ccd.28186

16. Lee R, Ben-Dor I. Revascularization methods in spontaneous coronary artery dissection: a focused review. *Cardiovasc Revasc Med*. (2017) 18(7):544–8. doi: 10.1016/j.carrev.2017.05.008

17. Uema A, Araki M, Sonoda S, Shimizu A, Kashiyama K, Muraoka Y, et al. Successful coronary intervention for spontaneous coronary dissection in a patient with fibromuscular dysplasia. *J Cardiol Cases*. (2013) 8(5):158–60. doi: 10.1016/j.jccase.2013.07.011

18. Noguchi M, Obunai K, Fukui Y, Okumura H, Watanabe H. Usefulness of cutting balloon angioplasty prior to stenting with intravascular ultrasound imaging guidance for spontaneous multi-vessel coronary artery dissection including the left main coronary artery. *Intern Med*. (2018) 57(13):1867–71. doi: 10.2169/internalmedicine.0177-17

19. Bastante T, Rivero F, Cuesta J, Del Val D, Roquero P, Alfonso F. Treatment of spontaneous coronary artery dissection with fenestration: clinical and angiographic follow-up. *Rev Esp Cardiol(English ed.)*. (2022) 75(2):177–9. doi: 10.1016/j.rec.2021.07.018

20. Macaya F, Yeoh J, Kanyal R, MacCarthy P, Byrne J. Haematoma decompression for a postpartum extensive left main spontaneous dissection. *Coron Artery Dis*. (2021) 32(4):352–3. doi: 10.1097/MCA.0000000000000992

21. Fujita H, Yokoi M, Ito T, Nakayama T, Shintani Y, Sugiura T, et al. Unusual interventional treatment of spontaneous coronary artery dissection without stent implantation: a case series. *Eur Heart J Case Rep*. (2021) 5(8):ytab306. doi: 10.1093/ehjcr/ytab306

22. Kahata M, Otsuka M, Kataoka S, Yazaki K, Kumagai A, Inoue K, et al. Successful angioplasty with intravascular ultrasound and optical frequency domain imaging guidance for tandem intramural hematoma caused by coronary artery spasm. *J Cardiol Cases*. (2017) 16(6):199–201. doi: 10.1016/j.jccase.2017.08.006

23. Cerrato E, Meynet I, Quadri G, Giacobbe F, Rolfo C, Tomassini F, et al. Acute interventional management of spontaneous coronary artery dissection: case series and literature review. *Int Cardiovasc Forum J*. (2018) 15:20-1. doi: 10.17987/icfj.v15i0.544

24. Mailey JA, Thompson P, Johnston PW, Owens CG. A complex case of pregnancy-related left main stem spontaneous coronary artery dissection. *Interventional Cardiology: Reviews, Research, Resources*. (2022) 17:e09. doi: 10.15420/icr.2021.33

25. Yamamoto T, Takaya T, Ishii T, Ishida A. ST-segment elevation myocardial infarction originating from the preceding spontaneous coronary artery dissection: a case report. *Cardiovasc Interv Ther*. (2023) 38(1):127–9. doi: 10.1007/s12928-022-00886-8

26. Choudhury T, Solomonica A, Bagur R, Lavi S. Intravascular imaging for cardiac arrest with "normal" coronary arteriography. *Cardiovasc Revasc Med*. (2018) 19(8):53–5. doi: 10.1016/j.carrev.2018.04.016

27. Somerville A, Weinberg A. Combined coronary stenting and cutting balloon angioplasty in the management of a postpartum spontaneous coronary artery dissection. *Circulation*. (2022) 146(Suppl 1):A12977. doi: 10.1161/circ.146.suppl_1.12977

28. Ejima E, Murasato Y. TCTAP C-140 acute coronary syndrome caused by spontaneous coronary artery dissection in a 32-year-old pregnant woman. *J Am Coll Cardiol*. (2015) 65(17S):S320–1. doi: 10.1016/j.jacc.2015.03.418

29. Gilpin TR, Dana A. The rare occurrence of severe fibrofatty plaque coexistent with spontaneous coronary artery dissection. *Cardiovasc Interv*. (2022) 15(14): e165–6. doi: 10.1016/j.jcin.2022.04.041

30. Low TT, Houdmont M, Sim HW, Chan KH, Loh PH, Loh JP. Spontaneous coronary artery dissection: clinical implications and diagnostic challenges. Overlooked and underappreciated in Asia? *Clin Cardiol*. (2020) 43(11):1240–7. doi: 10.1002/clc.23484

31. McConkey HZ, De Maria GL. Juxtaposition of urgent angioplasty results in spontaneous coronary artery dissection: a case report of fresh vs. organized intramural haematoma. *Eur Heart J Case Rep*. (2023) 7(6):ytad210. doi: 10.1093/ehjcr/ytad210

32. Alyamani M, Aziz A, Nagendran J, Welsh RC. Multi-vessel spontaneous coronary artery dissection in a patient with aortic dissection: a case report. *Eur Heart J Case Rep*. (2022) 6(7):ytac263. doi: 10.1093/ehjcr/ytac263

33. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best PJ. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol*. (2017) 70(4):426–35. doi: 10.1016/j.jacc.2017.05.055

34. Braverman AC, Mittauer E, Harris KM, Evangelista A, Pyeritz RE, Brinster D, et al. Clinical features and outcomes of pregnancy-related acute aortic dissection. *JAMA Cardiol*. (2021) 6(1):58–66. doi: 10.1001/jamacardio.2020.4876

35. Yip A, Saw J. Spontaneous coronary artery dissection—a review. *Cardiovasc Diagn Ther*. (2015) 5(1):37. doi: 10.3978/j.issn.2223-3652.2015.01.08

36. Hassan S, Samuel R, Starovoytov A, Lee C, Aymong E, Saw J. Outcomes of percutaneous coronary intervention in patients with spontaneous coronary artery dissection. *J Interv Cardiol*. (2021) 2021:2–6. doi: 10.1155/2021/6686230

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 10 November 2023
DOI 10.3389/fcvm.2023.1275725

OPEN ACCESS

EDITED BY
Pablo Avanzas,
Hospital Universitario Central de Asturias, Spain

REVIEWED BY
Matteo Nardin,
Asst degli Spedali Civili di Brescia, Italy
João Silva Marques,
Centro Hospitalar Universitário Lisboa Norte (CHULN), Portugal
Alessandra Chinaglia,
San Luigi Gonzaga University Hospital, Italy

*CORRESPONDENCE
Ivan Ilic
ivan1ilic@yahoo.com

RECEIVED 10 August 2023
ACCEPTED 23 October 2023
PUBLISHED 10 November 2023

CITATION
Ilic I, Radunovic A, Timcic S, Odanovic N, Radoicic D, Dukuljev N, Krljanac G, Otasevic P and Apostolovic S (2023) Drugs for spontaneous coronary dissection: a few untrusted options.
Front. Cardiovasc. Med. 10:1275725.
doi: 10.3389/fcvm.2023.1275725

Drugs for spontaneous coronary dissection: a few untrusted options

Ivan Ilic[1,2]*, Anja Radunovic[1], Stefan Timcic[1], Natalija Odanovic[1], Dragana Radoicic[1], Natasa Dukuljev[1], Gordana Krljanac[2,3], Petar Otasevic[1,2] and Svetlana Apostolovic[4,5]

[1]Department of Cardiology, Institute for Cardiovascular Diseases Dedinje, Belgrade, Serbia, [2]School of Medicine, University of Belgrade, Belgrade, Serbia, [3]Cardiology Clinic, University Clinical Center of Serbia, Belgrade, Serbia, [4]Cardiology Clinic, University Clinical Center Nis, Nis, Serbia, [5]School of Medicine, University of Nis, Nis, Serbia

Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome that is often overlooked, misdiagnosed, and maltreated. Medical treatment poses a significant challenge because of the lack of randomized studies to guide treatment. The initial clinical presentation should guide medical and interventional management. Fibrinolytic agents and anticoagulants should be avoided because they could favor hematoma propagation. In patients with SCAD, antiplatelet therapy should be prescribed especially dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel, whereas potent P2Y12 inhibitors, e.g., ticagrelor and prasugrel, should be avoided. If a stent was used, DAPT should be continued for 12 months. Aspirin only can be an option for patients without "high-risk" angiographic features—thrombus burden, critical stenosis, and decreased coronary flow. Beta-blocking (BB) agents should be used to prevent recurrence of SCAD. There is a general agreement that angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, mineralocorticoid antagonists, and loop diuretics should be used in patients with SCAD experiencing the symptoms of heart failure and a decrease in left ventricular ejection fraction below 50%. Although without firm evidence, statins can be used in SCAD due to their pleiotropic properties. The results of a randomized trial on the use of BB and statins are awaited. Aggregation of data from national registries might point out truly beneficial medications for patients with SCAD.

KEYWORDS

spontaneous coronary dissection, antiplatelets, beta-blocker, ACE inhibitor, statin

Introduction

Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome (ACS) that is often overlooked, misdiagnosed, and maltreated. The missed opportunities for timely diagnosis and adequate treatment come from a relatively small proportion of all ACS patients suffering from the condition, different pathophysiological mechanisms compared to atherosclerotic ACS, non-typical ACS patients (women aged 40–60 years of age without atherosclerotic risk factors), and procedural issues regarding interventional treatment. The confusion is further amplified by the misnomer "dissection" because the condition infrequently occurs as a consequence of a tear in the intimal layer that leads to blood accumulation in the media as was previously thought (inside–out theory). The dominant mechanism would be the rupture of *vasa vasorum* leading to hematoma formation in the media that compresses the coronary artery "true" lumen

(outside–in theory) (1, 2). The predisposing factors associated with the condition are female gender, peripartum period, and fibromuscular dysplasia (FMD), and the patients usually do not have traditional atherosclerotic risk factors—heredity, smoking, hypertension, diabetes, or dyslipidemia. Although it is relatively rare in the overall population of ACS patients undergoing coronary angiography (2%–4%), its incidence among ACS patients younger than 50 years of age rises to 25%. Emotional and physical stressors may contribute to the development of SCAD (2).

Knowing these facts about SCAD, it is no wonder that adequate treatment may not be easily conceived. Due to many uncertainties regarding the etiology and clinical and angiographic presentation of the disorder, medical treatment poses a significant challenge. This is further amplified by the lack of randomized studies and large registries that could generate sufficient data to guide treatment. Although timely reperfusion in the case of ST-elevation myocardial infarction (STEMI) is the ultimate goal, it may not be easily achieved in SCAD. Stent implantation may cause hematoma propagation proximal and distal from the initial site and further compromise the lumen. On the other hand, SCAD can occur in multiple coronary artery territories, so the decision about the appropriate treatment [percutaneous coronary intervention (PCI) or surgery] may be perplexing (3).

Antiplatelet therapy in SCAD treatment

In patients presenting with ACS, the currently recommended medical treatment consists of dual antiplatelet therapy (DAPT) with aspirin and a potent P2Y12 receptor inhibitor (4). However, this therapy could cause harm in patients with SCAD, unless this included stent implantation. Based on the pathophysiology of the disease, medical treatment should aim for the preservation of flow in the affected artery and cessation of hematoma propagation, which may be conflicting goals to achieve. Fibrinolytic therapy has been shown to extend the dissection and worsen prognosis in these patients (3).

The reason for DAPT use in patients with SCAD may be caused by an idea to achieve platelet inhibition to prevent thrombosis, which is in concert with current guidelines for ACS patients in general (4). In a Swiss cohort of 107 patients with SCAD, 90% of them received DAPT consisting of aspirin and clopidogrel in 51% of cases and aspirin and ticagrelor in 40% of cases, despite that only a minority of them underwent revascularization [seven PCI and one coronary bypass grafting (CABG)] (5). However, imaging studies using optical coherence tomography (OCT) failed to demonstrate a significant thrombus burden in patients with SCAD. In patients where hematomas were fenestrated and communicated with true lumen, the incidence of thrombus on OCT was little more than 30%, while in the so-called "non-fenestrated" cases, the thrombus was seen in only 14% of cases (1). Knowing the etiology of SCAD and the findings of imaging studies, the role of thrombus formation in this entity is probably not very important. On the other hand, ACS as a condition provokes prothrombotic mechanisms regardless of the causative mechanism of coronary artery occlusion and flow impairment. The narrowing of the vessel itself activates inflammatory and immune mechanisms that could further aggravate vessel thrombosis regardless of the initial pathway that led to coronary ischemia and ACS (6). This may be the rationale for continuing DAPT in SCAD patients. Although a relatively small registry by Feldbaum et al. (7) has demonstrated that increased use of DAPT, the expanding knowledge regarding the etiology of SCAD, and more frequent use of intravascular imaging, which led to the foundation of the non-atherosclerotic nature of the disease, could provide more evidence that the less aggressive antiplatelet regimen could be equally effective in this type of ACS. The importance of this topic and the lack of available evidence was recognized by the European Society of Cardiology (ESC), which has included it in the "gaps in evidence" of the recently published guidelines on ACS. It has been suggested that the way to overcome this issue would be to start a randomized trial to evaluate different antithrombotic strategies in patients with SCAD (4). Due to the relatively small proportion of these patients in the ACS population that are frequently unrecognized, we will have to wait for a while before reaching the recommendation for the use of antithrombotic agents in these patients.

One of the relatively large registries of SCAD patients including 23 centers in Italy and Spain has found that DAPT may be harmful to these patients. The "DIssezioni Spontanee COronariche (DISCO)" registry included 314 patients where 199 were treated conservatively, of which 67 (33.7%) were treated with single platelet therapy (SAPT) and 132 (66.3%) were prescribed DAPT. Mostly, DAPT consisted of aspirin and clopidogrel (63%), while 38% of patients were prescribed a combination of aspirin and a potent P2Y12 inhibitor ticagrelor. In the SAPT group, aspirin was given in 93% of patients and ticagrelor in 6% of patients. After 1 year, DAPT was associated with a higher rate of major adverse cardiac events (MACE) compared to SAPT (18.9% vs. 6.0%; HR 2.62, 95% CI 1.22–5.61, $P = 0.013$). The difference in MACE rate was mostly due to non-fatal myocardial infarction (15.2% vs. 3.0%; HR 3.20, 95% CI 1.33–7.69, $P = 0.009$) and unplanned PCI (12.1% vs. 1.5%; HR 3.69, 95% CI 1.36–9.91, $P = 0.01$). Most of the events occurred within 1 month after initial hospital admission, and in the multivariable analysis, the prescribed DAPT was an independent predictor of events and was associated with more than four times higher risk of MACE (HR 4.54; 95% CI 1.31–14.28; $P = 0.016$). Interestingly, bleeding events were neither very frequent in any group, nor was DAPT associated with higher bleeding rates (8). The higher incidence of MACE can be explained by early hematoma propagation and further aggravation of ischemia that required intervention in the DAPT group where a significant proportion of patients received potent P2Y12 inhibitors (2). Also, the most frequent type of SCAD in this registry was type 2, both 2A and 2B, which encompassed around 60% of the cases in both groups. This type can further aggravate more significant stenosis and ischemia due to hematoma propagation under potent DAPT. Noteworthy, the SAPT group had more type 4 SCAD (SAPT 26.9 vs. DAPT 16.0%), which will not probably progress and cause new adverse

events if left untreated (8). Other large registries have not found this association between antiplatelet therapy and MACE events. In a Swiss registry, almost 50% of patients received DAPT consisting of aspirin and ticagrelor or prasugrel. There was no difference in the MACE rate regarding the type of antiplatelet therapy prescribed (5).

A large Canadian registry that included 750 patients did not demonstrate adverse events related to the use of DAPT during 3 years of follow-up, although more than 80% of patients were treated conservatively. Over 90% were treated with aspirin, and 67.4% received clopidogrel or any other adenosine diphosphate (ADP) antagonist at hospital discharge. Interestingly in this large cohort, SCAD was confirmed using intracoronary imaging [intravascular ultrasound (IVUS), OCT] in less than 10% of cases, whereas 63.8% had preserved thrombolysis in myocardial infarction (TIMI) flow grade III at diagnostic coronary angiogram (9, 10).

When it comes to antiplatelet treatment in SCAD ACS, another important question arises: What is the optimal duration of DAPT? There is a consensus that patients who underwent PCI with stent implantation should be treated according to guidelines for ACS—12 months of DAPT (2, 4). On the other hand, it remains unknown how long to prescribe DAPT in patients who were treated conservatively after being diagnosed with SCAD and the ones who underwent balloon angioplasty with different kinds of devices (semi- or non-compliant balloons, scoring, or cutting balloons).

There is a clear trend toward spontaneous healing of SCAD lesions. We present the images of a 57-year-old female with treatment for hypertension, who presented with NSTEMI caused by SCAD in the left anterior descending territory. The patient underwent coronary angiography and was treated conservatively with DAPT consisting of aspirin and clopidogrel. Repeated coronary angiography and OCT showed angiographic healing and partial resorption of hematoma in previously healthy vessels (**Figure 1**).

The data from the Canadian registry, which included more than 150 patients who underwent repeated angiography on the average of 154 days (IQR 70–604 days), showed a resolution of stenosis in most cases with residual stenosis dropping to 25.5% (IQR 12.0%–38.8%) and only minority of the angiograms with decreased TIMI flow grade of less than 3—10/182 lesions (5.5%) in SCAD containing vessel. The authors stated that angiographic healing occurred in 157 of 182 lesions (86.3%). It is worth noting that angiographic healing occurred in 95% of lesions on coronary angiographies performed within 30 days of the event (11). The

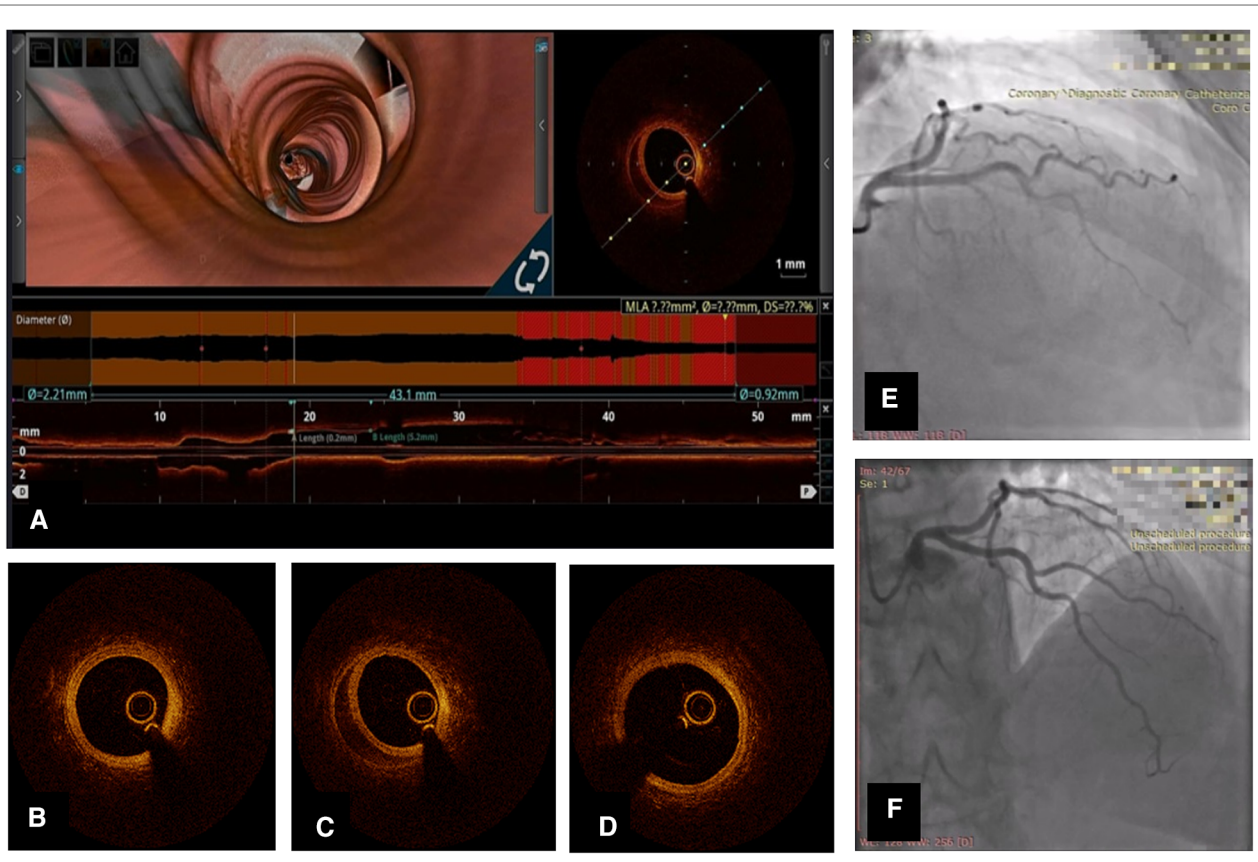


FIGURE 1
Coronary angiography and OCT of left anterior descending artery (LAD) SCAD in a 57-year-old lady. (**A**) Longitudinal OCT image 1 month after initial event with 3D flythrough showing persistent hematoma. (**B**) OCT cross-sectional image distal to SCAD lesion; (**C**) OCT cross-sectional at the level of hematoma; (**D**) OCT cross-section proximal to hematoma; (**E**) Coronary angiography of LAD [right anterior oblique (RAO)-cranial] at initial hospitalization; (**F**) Repeated coronary angiography 1 month later.

angiographic follow-up in patients in the Swiss registry also revealed a low incidence of persistent SCAD [3/68 patients (4%)] in the conservatively treated group that underwent angiography at a median of 6 months (IQR 5.5–6.5 months) (5). In both registries, the overall incidence of MACE was low, and in the Canadian registry post-discharge, MACE incidence was 8.4% after 3 years of follow-up, while in the Swiss registry after a median of 7.5 years, MACE events occurred in 15/105 patients (14.2%) (5, 10).

The duration of DAPT should be tailored according to the incidence and timing of MACE events in SCAD patients during follow-up. Large registries reported relatively low mortality during long-term follow-up in this group of ACS patients with estimated survival greater than 90%. However, the overall MACE rates in SCAD patients are relatively high due to recurrent spontaneous dissections and target vessel failure (TVF) after PCI (2, 5, 8–10, 12). What is notable is the high incidence of MACE during initial hospitalization and up to 1 month of follow-up (10). Repeated SCAD, whether an extension of the initial injury or a new affection in a different territory, is one of the major characteristics of the disease. Its reported incidence varies from 42 patients (5.6%) in the Canadian registry, 11/105 patients in the Swiss registry up to 17% in the US registry (5, 10, 12). All this has to be taken into account when planning an antiplatelet strategy in a SCAD patient.

Recently adopted new interventional strategies, such as balloon angioplasty using a "cutting" balloon or treatment with a thrombus aspiration catheter to induce a tear that would allow hematoma emptying, present another challenge in tailoring antiplatelet treatment of SCAD patients (13, 14). It seems reasonable to treat these patients similarly to the ones with atherosclerotic disease who underwent plain old balloon angioplasty (POBA) in the early days of interventional cardiology. The suggested regimen then was 1-month DAPT and continued aspirin afterward (15) (**Table 1**).

TABLE 1 Overview of registries of patients with SCAD regarding BB and antiplatelet agents.

Study (year of publication)	No. of subjects	Age (years)	Females (%)	Conservative treatment [*n* (%)]	BB [*n* (%)]	SAPT [*n* (%)]	DAPT [*n* (%)]	Clopidogrel in DAPT (%)	Other P2Y2 inhibitor [*n* (%)]	MACE [*n* (%)]	Bleeding events [*n* (%)]	Comments
Rogowski et al. (16) (2017)	64	53	94	56 (87)	55 (86)	5 (8)	59 (92)	44 (69)	15 (23)	5 (8)	NA	
García-Guimaraes et al. (17) (2021)	318	53	88	248 (78)	247 (79)	132 (41)	186 (59)	129 (41)	69 (22)	18 (6)	NA	In hospital f/up
Cerrato et al. (8) (2021)	314	52	89	199 (63)	157/199 (79)[a]	67/199 (34)[a]	132/199 (66)[a]	83/132 (63)[a]	49/132 (36)[a]	29/199 (14)[a]	2 (1)[a]	1 year f/up
Combaret et al. (18) (2021)	373	51	90	295 (79)	NA	NA	252/361 (69)	NA	NA	45 (12.3)	NA	
Seidl et al. (5) (2021)	105	53	93	97/105 (93)	83 (80)	10 (9)	95 (90)	48 (51)	47 (49)	15/105 (14)	NA	Median f/up 7.5 years
Daoulah et al. (19) (2021)	83	44	51	33 (40)	74 (89)	79 (97)	50 (61)	NA	NA	12 (14)	NA	Median f/up 18 month
Saw et al. (10) (2022)	750	51	88	(84)	632 (84)	244 (32)	505 (67)	NA	NA	105 (14)	NA	Median f/up 3 years

NA, not available.
[a]Conservatively treated group.

Fibrinolytics in SCAD treatment

Although fibrinolytic therapy represents an appropriate option in patients with STEMI that cannot be treated with an invasive strategy in a timely manner, it may pose a significant problem for the SCAD patients suffering from this form of ACS (4). Knowing the nature of the hematoma formation and the possible absence of visible thrombus on intravascular imaging, one could expect that giving a fibrinolytic agent in SCAD patients could be associated with hematoma propagation and new formation as we have previously documented (3). On the other hand, prolonged ischemia could cause irreversible damage to the myocardium subtended by the coronary artery affected with SCAD. Although there are case reports demonstrating the benefits of fibrinolytics in SCAD STEMI, ESC has, in the position statement, deemed fibrinolytics contraindicated in SCAD patients (2). However, it may sometimes pose a challenge to discern a SCAD patient from an atherosclerotic STEMI patient. It is on the clinician to weigh the potential risks and

benefits of fibrinolytic treatment in an unusual female STEMI patient without known atherosclerotic risk factors presenting with typical SCAD precipitating factors.

Anticoagulants in SCAD treatment

Most ACS patients receive anticoagulants according to current guidelines to treat ACS. After confirmation of SCAD using intravascular imaging, there is no indication to use anticoagulants, unless needed for prevention of thromboembolic events (atrial fibrillation, deep venous thrombosis). The same works for the patients who undergo PCI in SCAD, since relevant guidelines do not recommend anticoagulation after a successful PCI procedure (2, 4). This can be applied to most SCAD patients, but the ones that experience heart failure require mechanical circulatory support or mechanical ventilation and should be anticoagulated according to hospital protocols for the treatment of critically ill patients (20).

Beta-blockers in SCAD treatment

There is conflicting evidence regarding the use of beta-blockers (BB) in patients with SCAD despite intuitively beneficial effects on blood pressure and oxygen consumption reduction that could reduce the wall shear stress and contain the propagation of dissection. The idea to use BB in SCAD patients was extrapolated from the studies in patients with aortic dissection where the use of oral and intravenous BB had profound effects on morbidity and mortality (21). However, the etiological mechanisms are sometimes quite different between these two entities, except for aortic intramural hematoma that resembles the mechanism of SCAD formation.

The study by Saw et al. (22) demonstrated that the use of BB was associated almost threefold decreased risk of recurrent SCAD in a cohort of more than 300 patients, where the incidence of recurrent SCAD was around 10% and the authors specifically excluded the patients who were perceived with extension of previously diagnosed SCAD. However, the characteristics of this study group must be taken into account when discussing the use of BB in SCAD. Most of the patients presented as non-STEMI, whereas only a quarter of them had STEMI. Regarding risk factors, one-third of them were treated for hypertension, and a quarter had dyslipidemia. The average left ventricular ejection fraction (LVEF) was 57% with 21% with LVEF lower than 50%. Most of the patients had type 2 SCAD, and more than 60% of them had normal TIMI 3 flow (22). A recently published meta-analysis confirmed the beneficial effects of BB. The analysis that included 14 studies with more than 4,000 patients found that the use of BB (HR, 0.51; 95% CI, 0.33–0.77, $P = 0.0013$) was associated with a lower risk of SCAD recurrence (23). Based on these findings, BBs were used in more than 80% of patients long term in large contemporary registries (5, 8, 10). Despite compelling evidence on BB treatment in SCAD, their use could be limited by adverse effects such as bradycardia and hypotension, which may provoke vasospasm complicating conservatively treated SCAD. In patients with SCAD affecting the right coronary artery supplying the conduction system, BBs should be used with caution (**Table 1**).

We are awaiting the results of the first randomized trial on the use of BB and DAPT in patients with SCAD. This ambitious study, named BA-SCAD (BB and antiplatelet agents in patients with SCAD), plans to enroll around 600 patients in a 2×2 factorial design and randomize them to BB (yes/no) and a short course (1 month) and long course (12 months) of DAPT (24). The study will include only patients with LVEF greater than 50% since the ones with decreased systolic function should be treated according to current guidelines for myocardial infarction that recommend BB in patients with decreased LVEF (4).

The use of BBs in SCAD should be guided by measuring the potential benefits of their use against the risks and contraindications. In addition, one should bear in mind that SCAD patients are usually BB naïve and that treatment should be carefully tailored and monitored throughout the hospital stay.

Heart failure treatment in SCAD

There is a general agreement that angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), mineralocorticoid antagonists, and loop diuretics should be used in patients with SCAD experiencing the symptoms of heart failure with rise in natriuretic peptides and decrease in LVEF below 50% (2, 25). The use of heart failure therapy in SCAD patients with normal LVEF cannot be justified. The use of ACE inhibitors or ARBs differs in registries of SCAD patients. In the DISCO study, there were no data on the use of heart failure medications, while in the study by Saw and associates, ACE inhibitors/ARBs were used in more than 60% of patients at discharge and more than 40% of them remained on this therapy after 3 years (8, 10). Interestingly, in the Swiss registry, the patients who experienced adverse events were less often treated with ACE inhibitors/ARBs, the difference that did not reach statistical significance [3/15 (21%) vs. 41/90 (46%); $P = 0.09$] (5). However, a SAFER-SCAD study (statin and ACE inhibitor on symptoms in patients with SCAD) (NCT 02008786) might provide answers on heart failure medication use in SCAD. The study was registered in 2013, but unfortunately, there has not been a paper published on this design yet. The purpose was to measure invasively coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) in 40 SCAD patients at least 3 months after initial event and then to investigate prospectively in randomized fashion whether the addition of an ACE inhibitor or a statin to usual care in patients with ongoing chest pain and a CFR of <3.0 improves clinical status evaluated by Seattle Angina Questionnaire (SAQ) at 16 weeks compared to placebo (26). Since FMD has been frequently associated with SCAD, care should be taken when prescribing renin–angiotensin system inhibitors since there have been cases of significant renal artery stenosis associated with FMD (2, 27). These drugs should not

be linearly prescribed to SCAD patients before a thorough evaluation of associated conditions that may interfere with the intended treatment.

Statins in SCAD

Intuitively, adding a statin to the initial treatment of SCAD associated with ACS seems reasonable from the standpoint of their pleiotropic effects on inflammation and angiogenesis (28). However, simple extrapolation from atherosclerotic coronary artery lesions may not be entirely justified.

Despite the prevailing opinion that SCAD patients do not have traditional atherosclerotic risk factors, including dyslipidemia, the data from the large registries demonstrate that these patients can often suffer from this disorder. The DISCO registry revealed that 37.2% of patients had dyslipidemia prior to the SCAD event (8). On the other hand, in the largest registry from Canada, only 20.3% were diagnosed with lipid disorders (10). Surprisingly, there were more than 60% of patients with SCAD from the Swiss cohort who were diagnosed with lipid disorder with an average low-density cholesterol (LDL) of 3.3 ± 0.9 mmol/L (5). If you decide to add statin to the medical treatment of SCAD patients, another question arises—what are the target levels of LDL that we want to achieve in SCAD? Should we follow the guidelines for ACS mdash;"strike early and strike strong"—or should we initiate moderate-intensity statin and then adjust therapy according to the obtained results (29)? We might get some of the answers to these questions from the results of randomized trials of BA-SCAD and SAFER-SCAD, but still, some of the dilemmas on statin use in SCAD ACS will remain.

How to treat SCAD medically?

Before presenting an opinion on the optimal medical treatment of patients with SCAD, it is important to disclose that there is still no randomized data regarding any medical treatment of SCAD. Our suggestion will refer only to patients with confirmed SCAD on imaging study (OCT or IVUS). Due to the low recurrence of SCAD, therapy might be limited to a shorter period of time compared to atherosclerotic ACS.

Antiplatelet agents should be prescribed in patients with SCAD, especially DAPT consisting of aspirin and clopidogrel and limited to 1 month based on the high incidence of recurrence of intimal tear in this period after the initial event. In patients presenting with large thrombus burden, after balloon angioplasty with non-compliant or cutting balloon, it seems reasonable to prescribe DAPT consisting of aspirin and clopidogrel also for 1 month. However, in patients without "high-risk features" such as concomitant atherosclerosis, large thrombus burden, critical stenosis that was left untreated, and significant flow impairment in affected coronary arteries, it would be prudent to prescribe SAPT consisting of only aspirin. If the affected vessel was treated with stent implantation, DAPT should be prescribed according to the guidelines for up to 12 months after the event. The potent P2Y12 inhibitors such as ticagrelor or prasugrel should be avoided because the potential benefits of powerful platelet inhibition would be offset by the risk of hematoma propagation.

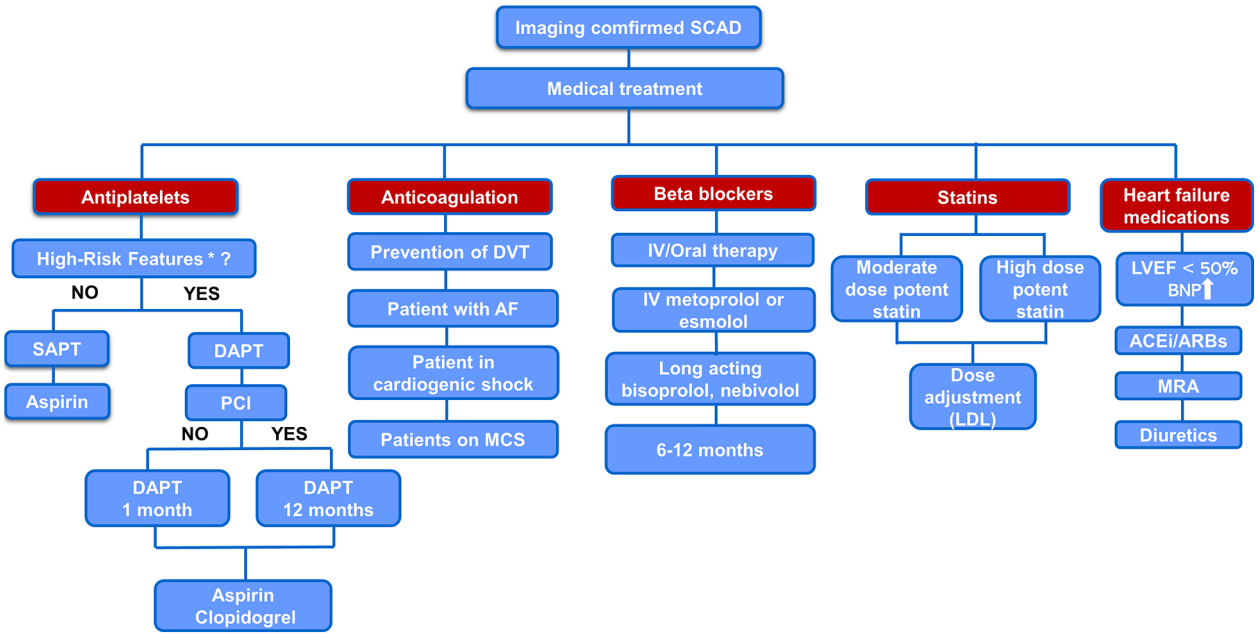


FIGURE 2
Proposed algorithm for medical treatment of imaging confirmed SCAD. *"high-risk" features—concomitant atherosclerosis, large thrombus burden, critical stenosis that was left untreated, and significant flow impairment in the affected coronary artery. AF, atrial fibrillation; BNP, brain natriuretic peptide; IV, intravenous; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist.

Anticoagulation should not be routinely prescribed in SCAD patients unless indicated for thromboembolic prevention of deep vein thrombosis (DVT) or in patients having an episode of atrial fibrillation. In addition, anticoagulation should be used, according to hospital protocols, in patients who experience cardiogenic shock and are mechanically ventilated or treated with mechanical circulatory support.

Based on available data, BB agents should be used in treating SCAD patients. Caution should be employed when starting BB therapy due to the risk of bradycardia and hypotension. The therapy may be started using intravenous formulations of metoprolol or esmolol initially and then switching to oral preparations and long-acting agents with dose titration. BB should be continued for at least 6–12 months bearing in mind the time interval necessary for spontaneous healing of SCAD lesions.

If heart failure develops, it is indicated to start ACE inhibitors/ARBs, mineralocorticoid receptor antagonists, and diuretics according to current guidelines. Since FMD is frequently associated with SCAD, in patients diagnosed with FMD presenting with SCAD, care should be taken to exclude renal artery stenosis when using ACE inhibitors/ARBs. In addition, usual care is necessary to avoid hypotension, volume depletion, and worsening of renal function when starting heart failure medications in SCAD patients.

There is no clear evidence on the use of statins in SCAD. Based on the available data regarding the effects of statins on inflammation and angiogenesis in SCAD and bearing in mind the low incidence of adverse events associated with lipid-lowering medications, we advocate selective lipid lowering with statins in SCAD patients, possibly high doses with close monitoring of the effects and adverse events (**Figure 2**).

Finally, it should be stated that optimal medical therapy for SCAD may not be easy to find despite the accumulation of evidence about its course and knowledge on disease pathophysiology. Probably, it will not be possible to have a randomized study that would encompass every aspect of medical treatment for this disease. Aggregation of data from national registries might point out truly beneficial medications for patients with SCAD.

Author contributions

II: Investigation, Writing – original draft. AR: Visualization, Writing – review & editing. ST: Software, Visualization, Writing – review & editing. NO: Investigation, Methodology, Writing – original draft. ND: Investigation, Data curation, Writing – original draft. DR: Resources, Formal analysis, Writing – review & editing. GK: Formal analysis, Resources, Writing – review & editing. PO: Supervision, Validation, Writing – review & editing. SA: Project administration, Supervision, Conceptualization, Writing – review & editing.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Jackson R, Al-Hussaini A, Joseph S, van Soest G, Wood A, Macaya F, et al. Spontaneous coronary artery dissection: pathophysiological insights from optical coherence tomography. *JACC Cardiovasc Imaging*. (2019) 12(12):2475–88. doi: 10.1016/j.jcmg.2019.01.015

2. Adlam D, Alfonso F, Maas A, Vrints C, Writing Committee. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. (2018) 39 (36):3353–68. doi: 10.1093/eurheartj/ehy080

3. Putniković B, Ilić I, Panić M, Aleksić A, Vidaković R, Nesković AN. Spontaneous coronary artery dissection—rare but challenging. *Vojnosanit Pregl*. (2014) 71 (3):311–6. doi: 10.2298/vsp120819055p

4. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Dan GA, et al. 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J*. (2023) 44 (38):3720–826. doi: 10.1093/eurheartj/ehad191

5. Seidl S, Rickli H, Rogowski S, Weilenmann D, Ammann P, Haager PK, et al. Long-term follow-up of medically treated patients with spontaneous coronary artery dissection: a prospective, Swiss single-centre cohort study. *Swiss Med Wkly*. (2021) 151:w30067. doi: 10.4414/smw.2021.w30067

6. Cimmino G, Loffredo FS, Morello A, D'Elia S, De Palma R, Cirillo P, et al. Immune-inflammatory activation in acute coronary syndromes: a look into the heart of unstable coronary plaque. *Curr Cardiol Rev*. (2017) 13(2):110–7. doi: 10.2174/1573403X12666161014093812

7. Feldbaum E, Thompson EW, Cook TS, Sanghavi M, Wilensky RL, Fiorilli PN, et al. Management of spontaneous coronary artery dissection: trends over time. *Vasc Med*. (2023) 28(2):131–8. doi: 10.1177/1358863X231155305

8. Cerrato E, Giacobbe F, Quadri G, Macaya F, Bianco M, Mori R, et al. Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry. *Eur Heart J*. (2021) 42 (33):3161–71. doi: 10.1093/eurheartj/ehab372

9. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, et al. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J*. (2019) 40(15):1188–97. doi: 10.1093/eurheartj/ehz007

10. Saw J, Starovoytov A, Aymong E, Inohara T, Alfadhel M, McAlister C, et al. Canadian spontaneous coronary artery dissection cohort study: 3-year outcomes. *J Am Coll Cardiol*. (2022) 80(17):1585–97. doi: 10.1016/j.jacc.2022.08.759

11. Hassan S, Prakash R, Starovoytov A, Saw J. Natural history of spontaneous coronary artery dissection with spontaneous angiographic healing. *JACC Cardiovasc Interv*. (2019) 12(6):518–27. doi: 10.1016/j.jcin.2018.12.011

12. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation*. (2012) 126:579–88. doi: 10.1161/CIRCULATIONAHA.112.105718

13. Fujita H, Yokoi M, Ito T, Nakayama T, Shintani Y, Sugiura T, et al. Unusual interventional treatment of spontaneous coronary artery dissection without stent implantation: a case series. *Eur Heart J Case Rep*. (2021) 5(8):ytab306. doi: 10.1093/ehjcr/ytab306

14. Spînu R, Belle L, Bonnet M, Cassar E, Mangin L. Aspiration technique in occlusive spontaneous coronary artery dissection. *EuroIntervention*. (2023) 19(4):e321–2. doi: 10.4244/EIJ-D-22-01055

15. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice guidelines. *Circulation*. (2022) 145(3):e18–114. doi: 10.1161/CIR.0000000000001038

16. Rogowski S, Maeder MT, Weilenmann D, Haager PK, Ammann P, Rohner F, et al. Spontaneous coronary artery dissection: angiographic follow-up and long-term clinical outcome in a predominantly medically treated population. *Catheter Cardiovasc Interv*. (2017) 89(1):59–68. doi: 10.1002/ccd.26383

17. García-Guimaraes M, Bastante T, Macaya F, Roura G, Sanz R, Barahona Alvarado JC, et al. Spontaneous coronary artery dissection in Spain: clinical and angiographic characteristics, management, and in-hospital events. *Rev Esp Cardiol (Engl Ed)*. (2021) 74(1):15–23. doi: 10.1016/j.rec.2020.04.002

18. Combaret N, Gerbaud E, Dérimay F, Souteyrand G, Cassagnes L, Bouajila S, et al. National French registry of spontaneous coronary artery dissections: prevalence of fibromuscular dysplasia and genetic analyses. *EuroIntervention*. (2021) 17(6):508–15. doi: 10.4244/EIJ-D-20-01046

19. Daoulah A, Al-Faifi SM, Alhamid S, Youssef AA, Alshehri M, Al-Murayeh M, et al. Spontaneous coronary artery dissection in the gulf: G-SCAD registry. *Angiology*. (2021) 72(1):32–43. doi: 10.1177/0003319720946974

20. Sharma S, Polak S, George Z, LeDoux J, Sohn R, Stys A, et al. Management of spontaneous coronary artery dissection complicated by cardiogenic shock using mechanical circulatory support with the Impella device. *Catheter Cardiovasc Interv*. (2021) 97:74–7. doi: 10.1002/ccd.28677

21. Nejim B, Mathlouthi A, Naazie I, Malas MB. The effect of intravenous and oral beta-blocker use in patients with type B thoracic aortic dissection. *Ann Vasc Surg*. (2022) 80:170–9. doi: 10.1016/j.avsg.2021.07.056

22. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol*. (2017) 70(9):1148–58. doi: 10.1016/j.jacc.2017.06.053

23. Chi G, Najafi H, Montazerin SM, Lee JJ. Factors associated with recurrent spontaneous coronary artery dissection: a systematic review and meta-analysis. *Coron Artery Dis*. (2022) 33(7):566–73. doi: 10.1097/MCA.0000000000001168

24. Alfonso F, de la Torre Hernández JM, Ibáñez B, Sabaté M, Pan M, Gulati R, et al. Rationale and design of the BA-SCAD (beta-blockers and antiplatelet agents in patients with spontaneous coronary artery dissection) randomized clinical trial. *Rev Esp Cardiol (Engl Ed)*. (2022) 75(6):515–22. doi: 10.1016/j.rec.2021.08.003

25. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. (2021) 42(36):3599–726. doi: 10.1093/eurheartj/ehab368

26. Sedlak T. Statin and angiotensin-converting enzyme inhibitor on symptoms in patients with SCAD (SAFER-SCAD). Available at: https://clinicaltrials.gov/ct2/show/NCT02008786?cond=scad&rank=6 (Accessed August 6, 2023).

27. Koratala A, Chamarthi G, Touyz RM, Dominiczak AF, Elijovich F, Spence JD, et al. Renovascular hypertension: one size does not fit all: challenges in diagnosis and management. *Hypertension*. (2021) 77(4):1022–8. doi: 10.1161/HYPERTENSIONAHA.121.17022

28. Zahedipour F, Butler AE, Rizzo M, Sahebkar A. Statins and angiogenesis in non-cardiovascular diseases. *Drug Discov Today*. (2022) 27(10):103320. doi: 10.1016/j.drudis.2022.07.005

29. Krychtiuk KA, Ahrens I, Drexel H, Halvorsen S, Hassager C, Huber K, et al. Acute LDL-C reduction post ACS: strike early and strike strong: from evidence to clinical practice. A clinical consensus statement of the Association for Acute Cardiovascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the European Society of Cardiology working group on cardiovascular pharmacotherapy. *Eur Heart J Acute Cardiovasc Care*. (2022) 11(12):939–49. doi: 10.1093/ehjacc/zuac123

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 27 November 2023
DOI 10.3389/fcvm.2023.1278453

OPEN ACCESS

EDITED BY
Tommaso Gori,
Johannes Gutenberg University Mainz, Germany

REVIEWED BY
Luca Bergamaschi,
University of Bologna, Italy
Valeria Paradies,
Maasstad Ziekenhuis, Netherlands

*CORRESPONDENCE
M. Kovacevic
mila.kovacevic@mf.uns.ac.rs

RECEIVED 16 August 2023
ACCEPTED 07 November 2023
PUBLISHED 27 November 2023

CITATION
Kovacevic M, Jarakovic M, Milovancev A, Cankovic M, Petrovic M, Bjelobrk M, Ilic A, Srdanovic I, Tadic S, Dabovic D, Crnomarkovic B, Komazec N, Dracina N, Apostolovic S, Stanojevic D and Kunadian V (2023) Contemporary review on spontaneous coronary artery dissection: insights into the angiographic finding and differential diagnosis. Front. Cardiovasc. Med. 10:1278453. doi: 10.3389/fcvm.2023.1278453

Contemporary review on spontaneous coronary artery dissection: insights into the angiographic finding and differential diagnosis

M. Kovacevic[1,2]*, M. Jarakovic[1,2], A. Milovancev[1,2], M. Cankovic[1,2], M. Petrovic[1,2], M. Bjelobrk[1,2], A. Ilic[1,2], I. Srdanovic[1,2], S. Tadic[1,2], D. Dabovic[1,2], B. Crnomarkovic[2], N. Komazec[2], N. Dracina[2], S. Apostolovic[3,4], D. Stanojevic[4] and V. Kunadian[5,6]

[1]Faculty of Medicine, University of Novi Sad, Serbia, [2]Cardiology Clinic, Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Novi Sad, Serbia, [3]Faculty of Medicine, University of Niš, Niš, Serbia, [4]Clinic for Cardiology, Clinical Center Niš, Niš, Serbia, [5]Faculty of Medical Sciences, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom, [6]Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

Spontaneous coronary artery dissection (SCAD), although in the majority of cases presents as an acute coronary syndrome (ACS), has different pathophysiology from atherosclerosis that influences specific angiography findings and enables most patients to be solved by optimal medical therapy rather than percutaneous coronary intervention (PCI). Therefore, accurate diagnosis is essential for adequate treatment of each patient as management of SCAD differs from that of ACS of atherosclerotic aetiology. So far, invasive coronary angiography remains the most important diagnostic tool in suspected SCAD. However, there are ambiguous cases that can mimic SCAD. In this review, the authors summarize current knowledge about the diagnostic algorithms, particularly angiographic features of SCAD, pitfalls of angiography, and the role of intracoronary imaging in the context of SCAD diagnosis. Finally, apart from the pathognomonic angiographic features of SCAD that are thoroughly discussed in this review, the authors focus on obscure angiography findings and findings that can mimic SCAD as well. Differential diagnosis and the timely recognition of SCAD are crucial as there are differences in the acute and long-term management of SCAD and other causes of ACS.

KEYWORDS

spontaneous coronary artery dissection, pregnancy, fibromuscular dysplasia, women's health, MINOCA

Introduction

Spontaneous coronary artery dissection (SCAD) is an important cause of myocardial infarction (MI) and sudden cardiac death in young adults, particularly women. It is defined as spontaneous, acute, or subacute development of an intramural hematoma (IMH) with or without a tear of the tunica intima, leading to the formation of a false lumen that is not caused by atherosclerosis, trauma, or coronary manipulation.

Compression of the true lumen leads to coronary insufficiency and typically presents with symptoms and signs of acute coronary syndrome (ACS) (1–3).

SCAD was first described in 1931 in the autopsy of a 42-year-old woman who died after a violent retching attack (4). Over the following decades, only isolated cases of SCAD were described, and with the development of invasive diagnostic and therapeutic procedures, it turned out that SCAD is much more frequent and challenging to diagnose and treat than previously thought (2).

Establishing an accurate diagnosis of SCAD as a cause of MI is challenging but, at the same time, crucial, given the different therapeutic approach compared to atherosclerotic ACS both acutely and in long-term follow-up (5, 6). Currently, invasive coronary angiography (ICA) is the gold standard for the diagnosis of SCAD, especially when combined with intracoronary imaging. However, it is associated with considerable risk of intramural hematoma and dissection propagation. Therefore, being non-invasive, computed tomographic coronary angiography (CTCA), with the improvement in techniques and protocols in recent times, has been emerging as a valid alternative to ICA for both diagnosis and even more for the follow-up (7, 8). Still, the main limitation of CTCA is the lower spatial resolution, which limits the evaluation of the distal segments of the coronary arteries, which are often affected in SCAD (9, 10). In addition, SCAD is a common coronary aetiology in the setting of MINOCA (Myocardial Infarction with Non-Obstructive Coronary Arteries) and cardiac magnetic resonance (CMR) could be useful to determine the nature of myocardial injury due to SCAD or other coronary differential diagnoses (11, 12).

Regarding the management, current European and American experts' consensus documents on SCAD recommend conservative treatment whenever possible, given the lower angiographic success and a higher complication rate of percutaneous coronary intervention (PCI) compared to those obtained in atherosclerotic disease (5, 13). Moreover, conservative treatment is associated with complete coronary healing in most cases and subsequently followed with favourable outcome (1, 5, 13–15). However, when indicated, particularly in SCAD patients presenting with STEMI and impaired coronary flow, PCI is inevitable, and effective in the substantial majority of patients, with similar in-hospital mortality and even better long-term outcomes compared with PCI for atherothrombotic STEMI (16, 17). These findings support the value of PCI in selected patients with SCAD.

In this review article, the authors summarize the current knowledge about the aetiology, epidemiology, pathophysiology, clinical presentation, risk factors, diagnostic algorithm, specifically the angiographic findings in SCAD, the angiographic pitfalls, the role of intracoronary imaging in the context of the diagnosis of SCAD and the currently recommended treatment.

Epidemiology

According to available data, SCAD is estimated to account for 1% to 4% of ACS cases overall, up to 35% of ACS events in women younger than 50 years (16), and 23% to 68% of ACS in pregnancy (18). SCAD has been reported, although rarely, in both young adults (under 25 years) and teenagers, especially if there is no pregnancy or hereditary connective tissue disease, and it is also scarce in very old patients (over 80 years) (19). The true prevalence and incidence in the general population is, for now, unknown. With technological advances and physician awareness of SCAD as a possible cause of ACS, its existence is increasingly being recognized (20).

Pathophysiology

The pathophysiology of SCAD is still hypothetical, and two mechanisms of its occurrence have been proposed based on imaging techniques and histopathology. The first "inside-out" mechanism explains that the tear in the tunica intima is responsible for the entry of blood and the separation of the tunica intima and tunica media. The second, more probable "outside-in" mechanism, explains that rupture of the vasa vasorum in the tunica adventitia is responsible for bleeding in the arterial wall leading to the formation of intramural hematoma (IMH). Either of these two mechanisms leads to acute or subacute false lumen formation which expands both longitudinally and circumferentially and compresses the true lumen leading to coronary ischemia and acute MI (21, 22).

Anticipating SCAD before coronary angiography

Although the definite diagnosis of SCAD can be made exclusively by performing coronary angiography, with or without the aid of intravascular imaging, there are some inciting factors, associated conditions, and precipitants that will point to possible SCAD diagnosis before coronary angiography is done. In particular, the link between female gender, pregnancy, fibromuscular dysplasia (FMD) and SCAD has been established in multiple series.

Female gender

According to available data collected from observational studies (**Table 1**), more than 90% of patients with SCAD are perimenopausal women, with an average age of 47–53 years, and a high percentage (90%) of associated FMD. Occurrence in men is less studied and shows different risk factors than in women, with 44% of cases associated with heavy lifting or isometric exercise. Men also report fewer traditional female-associated risk factors for SCAD, such as depression, anxiety, emotional stress, and migraines (34, 35).

Pregnancy and sex hormones

Pregnancy-related SCAD accounts for approximately 10% of SCAD cases. However, one-third of ACS in pregnancy and almost half of ACS in the postpartum period are due to SCAD. Furthermore, most pregnancy-related SCAD occur in the first

TABLE 1 The main contemporary case series with spontaneous coronary artery dissection (SCAD), clinical and angiographic presentation, initial management and the outcome.

Authors	Year	Patients *N*	Female gender *N* (%)	Initial presentation STEMI/ NSTEMI *N* (%)	SCAD type 1/2/3/4 *N* (%)	ICI total N (%)	Initial medical therapy *N* (%)	Crossover to revasc. *N* (%)	PCI CABG *N* (%)	In-hospital mortality *N* (%)	FU	FU mortality *N* (%)	Recurrent SCAD *N* (%)
Alfonso et al. (15)	2012	45	9 (82)	18 (40) 16 (36)	NA	14 (31.1)	36 (80)	7 (19.4)	8 (17.8) 1 (2.2)	1 (2.2)	730 day[a]	1 (2.2)	2 (4.4)
Saw et al. (23)	2014	168	155 (92.3)	44 (26.1) 124 (73.9)	59 (29.1) 136 (67) 8 (3.9)	NA	139 (82.7)	6 (4.3)	28 (16.7) 1 (0.59)	0	6.9 years[a]	4 (2.4)	22 (13.1)
Tweet et al. (14)	2014	189	174 (92)	111 (58.7) 77 (40.7)	NA	24 (13)	94 (49.7)	8 (8.5)	89 (47.1) 6 (3.2)	1 (0.53)	2.3 years[a]	1 (0.5)	27 (14.3)
Lettieri et al. (24)	2015	134	109 (81)	66 (49.2) 54 (40.3)	NA	NA	78 (58.2)	2 (2.6)	51 (38.1) 5 (3.73)	3 (2.2)	22 months[a]	8 (5.9)	6 (4.7)
Nakashima et al. (16)	2016	63	59 (94)	55 (87) 8 (13)	27 (43) 35 (55) 1 (2)	41 (65.1)	28 (44.4)	0	34 (54) 1 (1.6)	NA	50 month[a]	1 (0.63)	17 (27)
McGrath-Cadell et al. (25)	2016	40	38 (95)	12 (30) 26 (65)	NA	NA	27 (67.5)	0	12 (30) 1 (2.5)	0	16 month	0	3 (8)
Faden et al. (26)[b]	2016	79	79 (100)	42 (53.2) 24 (30.4)	NA	NA	27 (34.2)	NA	31 (39.2) 23 (29.1)	3 (3.8)	NA	NA	NA
Rogowski et al. (27)	2017	64	60 (94)	19 (30) 44 (69)	32 (47.8) 32 (52.2)	NA	56 (87.5)	0	7 (10.9) 1 (1.6)	1 (1.6)	5.9 years[a]	0	3 (4.7)
Saw et al. (28)	2017	327	297 (90.8)	84 (25.7) 243 (74.3)	99 (25.6) 270 (69.8) 18 (4.7)	NA	272 (83.2)	9 (3.3)	54 (16.5) 7 (2.14)	0	3.1 years[a]	1 (0.3)	9 (2.8)
Clare et al. (29)	2019	208	185 (88.9)	41 (19.7) 167 (80.3)	NA	NA	176 (84.6)	NA	9 (4.3) 23 (11.1)	NA	1 years	5 (2.4)	22 (10.6)
Mori et al. (30)	2021	302	267 (88.4)	145 (48) 136 (45)	52 (17.2) 149 (49.3) 20 (6.6) 81 (26.8)	91 (30.1)	198 (65.6)	NA	100 (33.1) 4 (1.3)	1 (0.3)	22 month[a]	1 (0.3)	10 (3.3)
Saw et al. (31)	2022	750	664 (88.5)	223 (29.7) 524 (69.9)	291 (29) 603 (60.2) 108 (10.8)	57 (7.6)	648 (86.4)	15 (2.3)	104 (13.9) 5 (0.7)	1 (0.1)	3 years	5 (0.7)	18 (2.4)
Garcia Guimaraes et al. (32)	2022	389	344 (88)	211 (54) 156 (40)	84 (19) 271 (62) 38 (9) 48 (11)	93 (24)	305 (78.4)	10 (3.3)	84 (21.6) 0 (0%)	7 (1.8)	29 month	9 (2.5)	7 (2)
Jensen et al. (33)	2023	186	108 (81)	80 (43) 106 (57)	NA	NA	134 (72)	NA	43 (23.1) 9 (4.8)	NA	4.5 years[a]	9 (4.8)	42 (22.6)

The Table reports all studies that included more than 40 patients.

STEMI, ST segment elevation myocardial infarction; NSTEMI, Non ST segment elevation myocardial infarction; SCAD, spontaneous coronary artery dissection; PCI/CABG, percutaneous coronary artery intervention/coronary artery bypass graft; MI, myocardial infarction; FU, follow-up; NA, not applicable; y, year, m, month; d, day;.

[a]median.

[b]SCAD in pregnancy; ICI, intracoronary imaging.

10.3389/fcvm.2023.1278453

week after delivery, when estrogen and progesterone levels decline (3, 36). This association with pregnancy highly suggest a pathophysiological role of female sex hormones. However, this hormonal hypothesis has been challenged by a few studies demonstrating that the rate of hormonal contraception, hormone replacement therapy, nulliparity and multiparity did not differ between SCAD patients and the general population (13, 37). It is also unclear whether the absolute levels or fluctuations in circulating estrogen and progesterone influence the SCAD the most. Furthermore, estrogen level reduction in the premenstrual, late luteal phase, has been studied in patients with coronary vasospasm and migraines (38, 39). The precise nature of this relationship remains to be elucidated but may relate to changes in the intima-media composition, vessel microvasculature or vascular connective tissue.

Systemic connective tissue diseases

Patients with systemic connective tissue diseases associated with arteriopathy or arterial dissection, such as Marfan, Ehlers-Danlos, and Loeys-Dietz syndrome, account for less than 5% of SCAD patients (6). According to registries, more than 50% of patients with SCAD who underwent imaging for extra-coronary vascular abnormalities have FMD. It is defined as a non-inflammatory, non-atherosclerotic condition diagnosed primarily in women and characterized by abnormal proliferation of one or more layers of the arterial wall, resulting in arterial stenosis, dissection, and aneurysms of medium-sized arteries. Other vascular findings in patients with SCAD include cerebral and visceral aneurysms, dissections, pseudoaneurysms, and arterial tortuosity in patients with and without diagnostic criteria for FMD. Analysis of several cohort studies concluded that systemic inflammatory diseases are associated with SCAD in less than 5% of cases, unlike FMD (19, 40).

Genetics

Although genetic predisposition is suggested in a very small number of cases, including first- and second-degree relatives, SCAD does not appear to be a strongly inherited condition. The association of SCAD with congenital connective tissue diseases and arteriopathies has been described, however, genetic mutations are rare and are most often expressed in Ehlers-Danlos, Loeys-Dietz, Marfan syndrome, Autosomal dominant polycystic kidney disease and Pseudoxanthoma elasticum. Although no single SCAD gene has been described yet, research has identified individual risk loci with potential genes that carry a biological and pathophysiological risk, including those associated with FMD and other vascular disorders. Routine genetic testing is not currently recommended but may be considered in SCAD survivors with suspected connective tissue diseases or hereditary arteriopathies (3, 41).

Migraines

The results of several studies have shown that endothelial dysfunction in migraine plays a role in conditions such as stroke and cervical arterial dissection, which correlates with the pathophysiology of SCAD (42, 43).

Emotional or physical stress as precipitating factors

Up to two-thirds of patients with SCAD have a history of stressors that preceded chest pain. In women, it is most often emotional stress, while in men it is most often physical stress, including isometric exercises and heavy lifting. One hypothesis is that these precipitating factors lead to a catecholamine storm, which increases coronary afterload leading to intimal rupture or vasa vasorum disruption (44, 45). Similar pathophysiologic mechanism is believed to be responsible for Takotsubo cardiomyopathy, influencing some overlap in the clinical presentations of these two entities. Moreover, there are described cases with both conditions in the same setting (45, 46).

Clinical presentation

SCAD most commonly presents with chest pain and other common symptoms of ACS, with electrocardiographic changes directing to MI with ST-segment elevation (STEMI) registered in 26-58.7% of cases overall and up to 75% in pregnancy-associated SCAD (14, 28, 47, 48). However, SCAD can also present as cardiogenic shock, ventricular arrhythmias or sudden cardiac death (49, 50). SCAD patients are younger, more often female, and have fewer traditional cardiovascular risk factors than patients with atherosclerotic ACS. Pregnancy-related SCAD has a more severe clinical course and usually presents as STEMI, particularly anterior, with left main and multivessel involvement (48, 51). Therefore, resulting in a more extensive myocardial injury, it is associated with an increased incidence of cardiogenic shock requiring mechanical circulatory support, and cardiac transplantation, leading to a higher maternal and fetal mortality rate (48). The presence or absence of traditional cardiovascular risk factors is not very useful for examining the likelihood of SCAD. Despite the low burden of common risk factors compared to atherosclerotic ACS, patients with SCAD are not free of them. The prevalence of hypertension is about 30%, dyslipidemia is present in a range of 20%–35%, while diabetes is uncommon (less than 5%) (37, 48, 52). However, it is documented that the younger the patient is and the lower the number of traditional risk factors, the greater the probability of SCAD (52).

Angiographic finding in SCAD

To establish the diagnosis of SCAD, apart from common ACS clinical presentation and predisposing factors such as female gender and FMD that can increase the likelihood of SCAD, coronary angiography with or without adjunctive intravascular imaging is still crucial for accurate diagnosis. Nevertheless, three typical angiographic patterns of SCAD were proposed by Saw to aid the diagnosis (22, 53).

Type 1 accounts for about one-third of cases (16, 54), and represents the pathognomonic finding with multiple radiolucent lumen of linear filling defect (recognizable true and false lumen), usually with contrast dye staining in the false lumen. This

appearance of SCAD is caused by the presence of an intimal tear which is identified in approximately 30% of SCAD cases (**Figure 1**, **Figure 2A**).

Type 2 is the most common pattern (two-thirds of cases, **Table 1**) (16, 54), characterized by an abrupt change in the arterial calibre causing long and smooth stenosis caused by IMH, that tapers distally. It is located predominantly in the transition from mid to distal segments, most frequently affecting LAD. It is divided into Type 2a when there is restoration of the normal vessel in the distal segment (**Figure 1**, **Figure 2B**), and Type 2b, when the stenosis extends till the end of the artery (**Figure 1**, **Figure 2C**).

Type 3 is the least common (less than 5%) (16, 54), resembles atherosclerotic plaque with underlying focal, more localized IMH, thus difficult to diagnose without the assistance of intravascular imaging (**Figure 1**, **Figure 2D**).

This Yip-Saw classification (22) is mainly focused on the most common angiographic findings and is particularly helpful in recognizing Type 2 SCAD once interventional cardiologists become familiar with the pattern. Some authors, however, prefer the pathological description (presence of intimal tear or *fenestrated SCAD* vs. IMH or *non-fenestrated SCAD*) over Yip-Saw "type" classification, given the finding of a retrospective studies showing that isolated IMH (corresponding to angiographic SCAD type 2 and 3) carries a higher risk of SCAD extension and clinical deterioration, while intimal tear (fenestrated SCAD, angiographic type 1) may have a protective role in some patients possibly via decompression of IMH into the lumen (23, 30, 32). Although the registries have found increased incidence of MACE in patients with IMH type of SCAD the burden of evidence does not allow to discriminate this type as the one with higher risk of events. Detailed evaluation with intracoronary imaging is needed to define its type and to identify high-risk features associated with more adverse events. Furthermore, SCAD is a highly dynamic process, fenestrated and non-fenestrated SCAD may be considered as two distinct pathological manifestations of the same substrate, with IMH that may precede intimal tear, which is consistent with the "outside-in" theory of SCAD occurrence. Therefore, for better understanding and decision-making process, Yip-Saw classification (22) is the preferred one.

Recently, additional Type 4 SCAD has been proposed to describe total occlusion, usually of a distal vessel, a pattern particularly challenging to diagnose (**Figure 1**, **Figure 2E**) (55).

However, all these types can coexist in the same vessel, generating hybrid types (**Figure 2F**).

Although SCAD has been reported in all coronary arteries, sporadically even simultaneously (contiguous or non-contiguous), LAD is the most affected artery (5, 24, 54). Regarding coronary segments, SCAD has a predilection for more distal coronary segments (5, 54) in contrast to atherosclerosis, particularly Type 2 and 4 SCAD. On the contrary, type 1 SCAD generally affects proximal segments. Another angiographic feature favouring SCAD is the absence of atherosclerotic lesions in coronaries unaffected by SCAD (5, 52). Furthermore, the angiographic ambiguity of SCAD is constrained by side branches, which appear to provide resistance to further longitudinal extension (52). It is also demonstrated that SCAD happens more often in patients with tortuous arteries. Moreover, severe tortuosity (≥2 consecutive curvatures ≥180°) was associated with a three times higher risk of recurrent SCAD (10).

Differential diagnosis of SCAD

Although the angiographic features of SCAD are characteristic, several potential pitfalls and essential differential diagnoses should be considered.

Type 1 angiographic appearance of SCAD is pathognomonic, usually developing in the late disease course, probably due to decompression of the false lumen hematoma into the true lumen. However, this angiographic finding has several mimickers, such as spontaneous recanalized coronary thrombus (SRCT) (56, 57) (**Figures 3, panels B1, 2**), atherosclerotic plaque rupture or erosion with apposition of thrombi (**Figures 3, panels C1, 2**), or even iatrogenic coronary dissection (**Figures 3, panel D**).

SRCT is a rare condition characterized by multiple communicating channels divided by thin septa, usually termed a "honeycomb-like" structure, "lotus root" appearance, or "Swiss cheese" pattern. The proposed mechanism of SRCT is the recanalization of an in-situ thrombus, formating several lumens which differ in size. To distinguish these two diagnoses, high-resolution intracoronary imaging techniques, intravascular ultrasound (IVUS) or optical coherence tomography (OCT), can be helpful (**Figures 3, panels B1–2**). Interestingly, "lotus root" pattern was recently observed in a patient with SCAD, possibly as a result of uncommon remodelling and healing pattern of subacute or chronic SCAD. (58)

Rupture or erosion of atherosclerotic plaque resulting in intraluminal thrombus formation can mimic type 1 SCAD as well (**Figures 3, panels C1–2**). Furthermore, contrast penetration into the atherosclerotic plaque core causing a localized plaque-associated dissection can resemble contrast penetration into the false lumen of a Type 1 SCAD. Although intraluminal thrombus might be seen in the occlusive (Type 4) SCAD, the presence of substantial thrombus and distal embolization should divert diagnosis to ACS caused by typical mechanisms, atherosclerotic plaque rupture or erosion. These two entities, although resembling angiographically, can be easily separated by intravascular imaging techniques (**Figures 3 A1–2, C1–2**).

Another feature similar in angiographic appearance to type 1 SCAD is iatrogenic coronary artery dissection (**Figures 3, panel D**). Furthermore, SCAD is associated with an increased risk for iatrogenic dissection (59), either due to the vulnerability of such coronary artery with predisposing arteriopathies, particularly FMD or due to the injury of thin intima with preexisting hematoma. Both deep guiding catheter intubation and the jet of contrast injection can make a tear into the vessel wall creating a typical picture of a dual (true and false) lumen. Other mimickers of SCAD type 1 include different contrast flow patterns simulating a linear filling defect, usually due to insufficient contrast volume or flow, and can easily be distinguished from SCAD by an experienced interventional cardiologist and by giving a more fulsome, generous contrast injection.

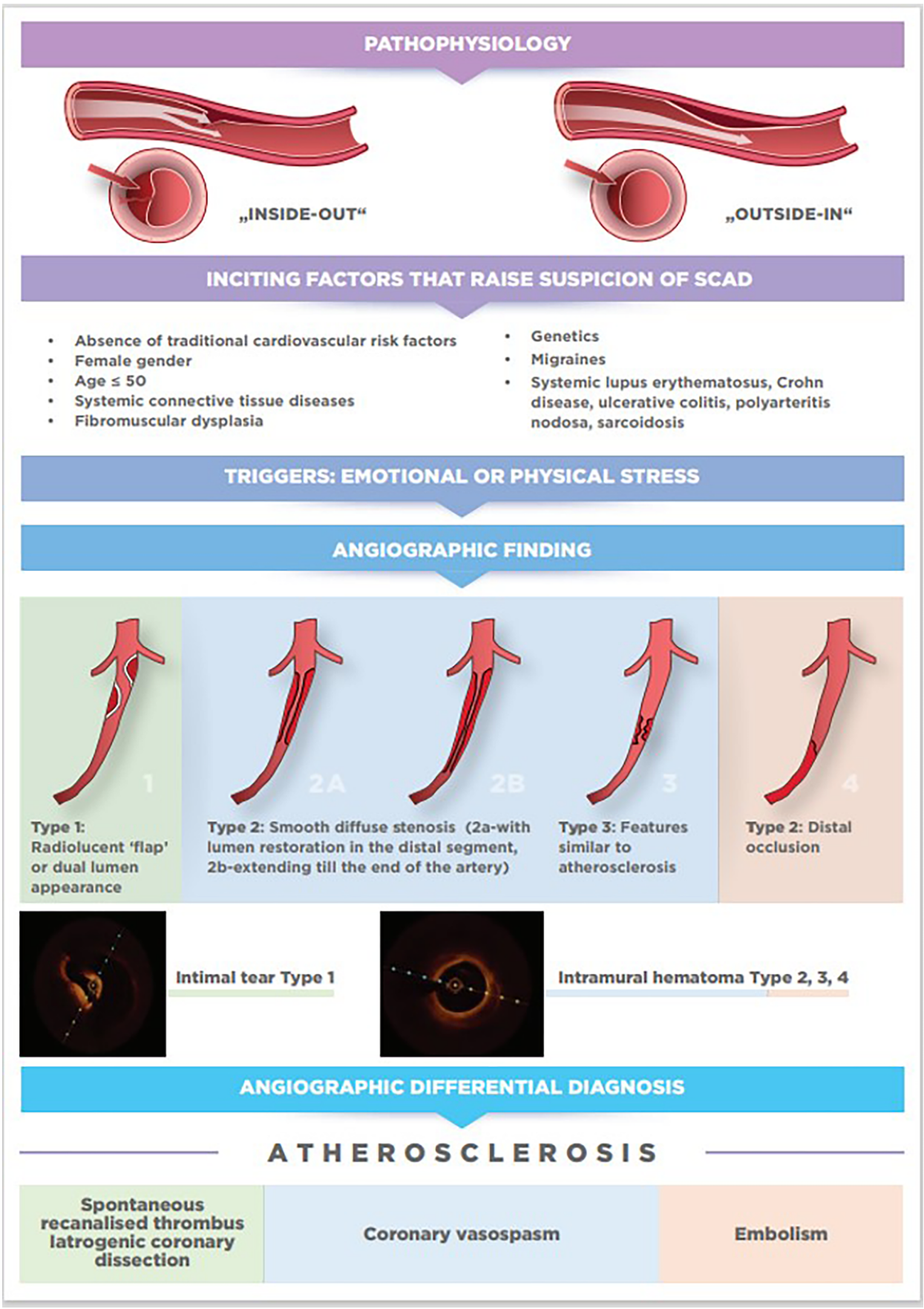


FIGURE 1
From pathophysiology to diagnosis.

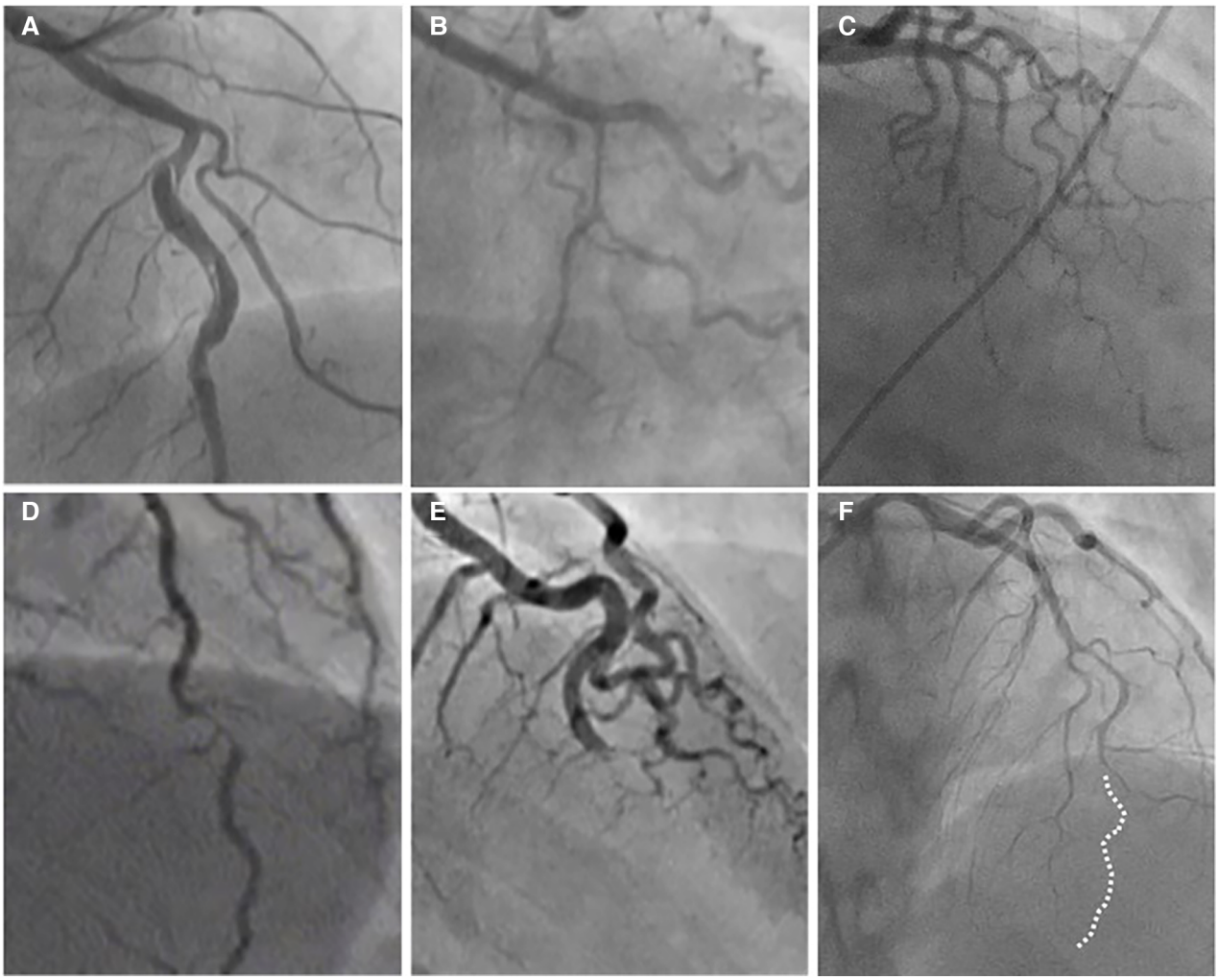


FIGURE 2
The angiographic appearance of SCAD. (A) Type 1-recognizable radiolucent flap; (B) type 2a-smooth diffuse stenosis with lumen restoration in the distal segment; (C) type 2b-smooth diffuse stenosis extending till the end of the artery; (D) type 3-resembling atherosclerosis; (E) type 4-distal occlusion; (F) an example of hybrid type SCAD- Type 2 in mid to distal segment with the transition to the Type 4-distal occlusion (dotted line depicts missing LAD).

Type 2 SCAD is the most common (Table 1), angiographically displayed with long and smooth stenosis. The most common mimickers of SCAD type 2 are coronary vasospasm and atherosclerosis. Coronary vasospasm can be focal, resembling SCAD type 2a or diffuse, extending distally as in type 2b SCAD. However, intracoronary nitroglycerine administration can reveal coronary vasospasm without difficulties (Figure 4).

Atherosclerosis is the most common differential diagnosis of Type 2, particularly Type 3 SCAD. Short stenosis with underlying hematoma in Type 3 SCAD is often misdiagnosed by coronary angiography unless an intravascular imaging technique is used (Figure 5). Intravascular ultrasound (IVUS) and optical coherence tomography (OCT), each with specific advantages and disadvantages, are valuable for diagnostic uncertainties. IVUS, as the first intravascular imaging device that was introduced in 1980s (60), has greater depth penetration, enabling complete visualization of the vessel wall to the external elastic lamina. At the same time, it has limited spatial resolution (150 μm) and is insufficient to distinguish SCAD from lipid-rich atheroma and for identification of subtle features associated with SCAD (intimal-medial membrane, small fenestrations between true and false lumens) (Figure 6). A typical IVUS feature, the white-black-white appearance (1) of the intimal-medial membrane, is pathognomonic for SCAD but not often seen. However, the main advantage of IVUS is that complete blood clearance with high-pressure contrast injection is not required. On the other side, OCT has the edge over IVUS due to the higher spatial resolution (15 μm), which enables to identify SCAD related features (61), distinguishing true and false lumen, the extent of the false lumen, whether it is circumferential or not, the "entry points" connecting true and false lumen, presence of intraluminal thrombi (Figure 7). The main pitfall of OCT is the necessity of blood clearance with a high-pressure contrast injection which portends the risk of false lumen extension, particularly in Type 1 SCAD.

Recently described, Type 4 SCAD, characterized by a total occlusion of a distal vessel, is particularly ambiguous, usually

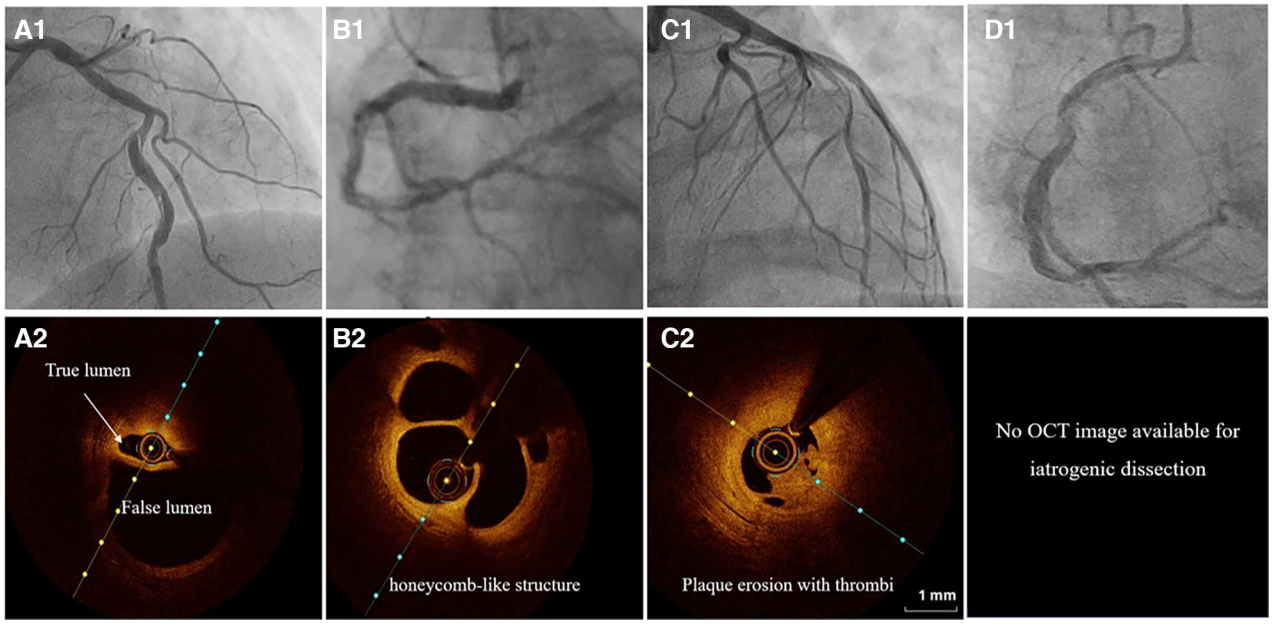


FIGURE 3
The angiographic differential diagnosis for type 1 SCAD. (**A1**) Type 1 SCAD with linear filling defect in mid-LAD. (**A2**) OCT finding in Type 1 SCAD- clear evidence of a small true (arrow) and a big false lumen with the OCT probe situated in the true lumen. (**B1**) Angiographic finding in spontaneous recanalized coronary thrombus (SRCT) in the mid and distal right coronary artery resembles SCAD. (**B2**) OCT finding in SRCT depicts a typical honeycomb-like structure. (**C1**) Angiographic finding in atherosclerotic acute coronary syndrome with plaque erosion and subsequent thrombus apposition. (**C2**) OCT finding corresponding to panel C1 with evidence of plaque erosion and intraluminal thrombi. (**D**) Angiographic finding in iatrogenic coronary dissection caused by guiding catheter, a picture resembling SCAD Type 1.

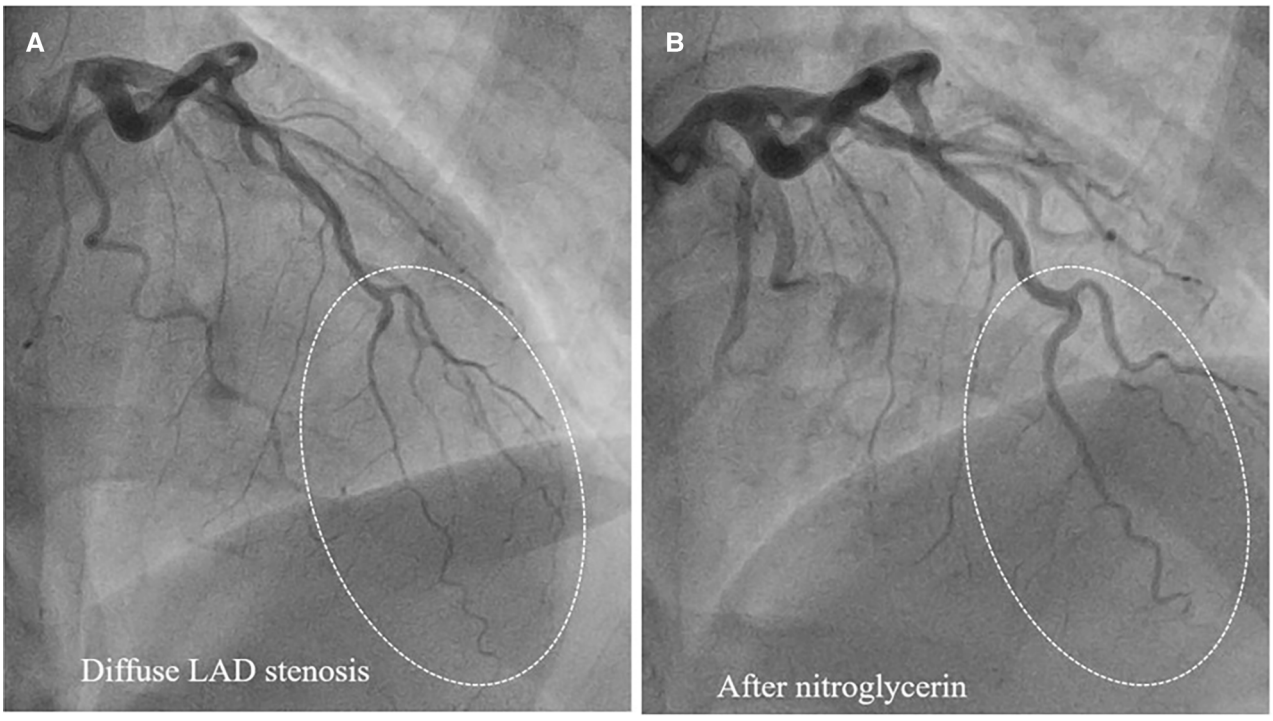


FIGURE 4
Epicardial coronary vasospasm mimics type 2 SCAD. (**A**) Diffuse LAD stenosis resembling Type 2 SCAD. (**B**) Restoration of vessel lumen after nitroglycerin administration confirms the epicardial vasospasm diagnosis.

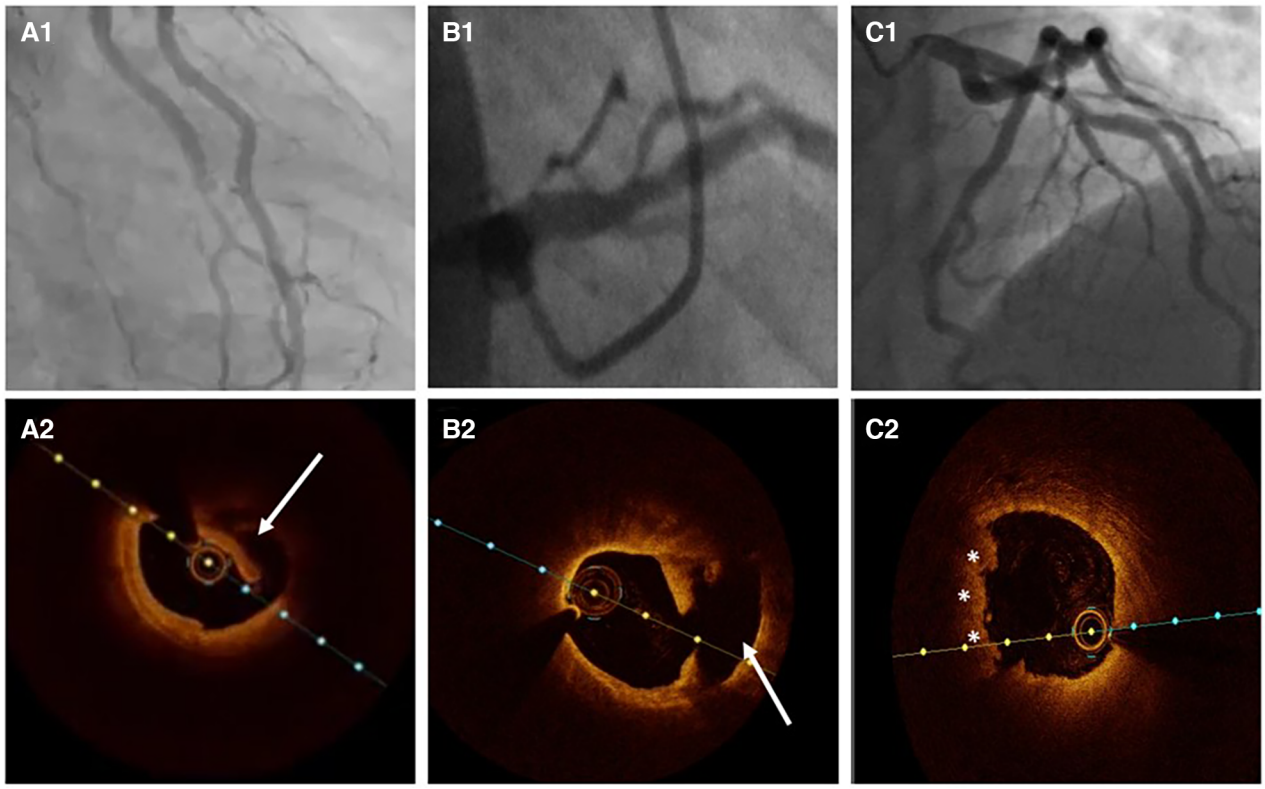


FIGURE 5
Atherosclerosis versus SCAD. (A1) Ramus intermedius lesion resembling atherosclerotic plaque rupture. (A2) OCT image demonstrating SCAD with intima-media complex dehiscence (arrow). (B1) Left anterior descending (LAD) lesion in proximal segment. (B2) OCT evidence of atherosclerotic plaque rupture (arrow). (C1) Haziness in proximal LAD. (C2) Plaque erosion with apposition of thrombi (asterisks).

misdiagnosed as atherosclerotic plaque rupture with thrombus formation as in STEMI and thus systematically treated with PCI. Coronary embolization from an upstream source of thrombi, such as prosthetic, mechanical valves or rheumatic valves, coronary aneurysms, or paradoxical embolization, can mimic Type 4 SCAD as well. Nevertheless, thorough anamnesis, inciting risk, and precipitating factors can raise suspicion of SCAD. Restoration of blood flow after wiring the artery can unmask typical SCAD features and, if combined with intracoronary imaging techniques, might enable definite SCAD diagnosis. If treated conservatively afterwards, complete vessel healing follows the natural SCAD process. Additionally, Type 4 frequently coexists with other types, either following Type 1, which can be the source of an embolus or continuing to other types, in which case IMH proximal to the occlusion can be detected by intravascular imaging techniques (**Figure 8**). SCAD progression from Type 1, 2 or 3 to Type 4 is also possible, particularly during a watchful waiting strategy in severe forms of SCAD (**Figure 9**).

Management

Given the complex pathophysiology of SCAD and the natural tendency for spontaneous healing, conservative management is the recommended strategy in stable SCAD. In contemporary cohorts (**Table 1**), conservative management was successful in more than 80% of medically managed patients (37), with angiographic evidence of healing within weeks to months (14, 27). Furthermore, revascularization with PCI is associated with a higher complication rate and a lower procedural success rate and does not protect against repeat revascularization or recurrent SCAD (14).

The goal of medical therapy early after SCAD diagnosis is to relieve the symptoms (particularly chest pain), manage blood pressure and to prevent SCAD extension and recurrence. Due to the lack of randomized trials, management is primarily based on expert consensus.

Although SCAD presents with ACS, if not treated with PCI, due to the distinct pathophysiology from atherosclerotic ACS, the use and duration of dual antiplatelet therapy (DAPT) is controversial. On the one hand, it is believed that the presence of intimal tear can be prothrombotic, influencing, though very rarely, luminal thrombus formation (62), justifying DAPT (acetylsalicylic acid and clopidogrel) in the acute phase. On the other hand, IMH propagation can be stimulated with antiplatelet and anticoagulant medication. Therefore, the general consensus is to avoid anticoagulant therapy and to shorten DAPT duration (up to 4 weeks) (6, 13) unless there is an unequivocal indication for anticoagulant treatment (atrial fibrillation, left ventricular thrombus). Long-term acetylsalicylic acid may be reasonable in patients with FMD or evidence of atherosclerosis on intravascular imaging.

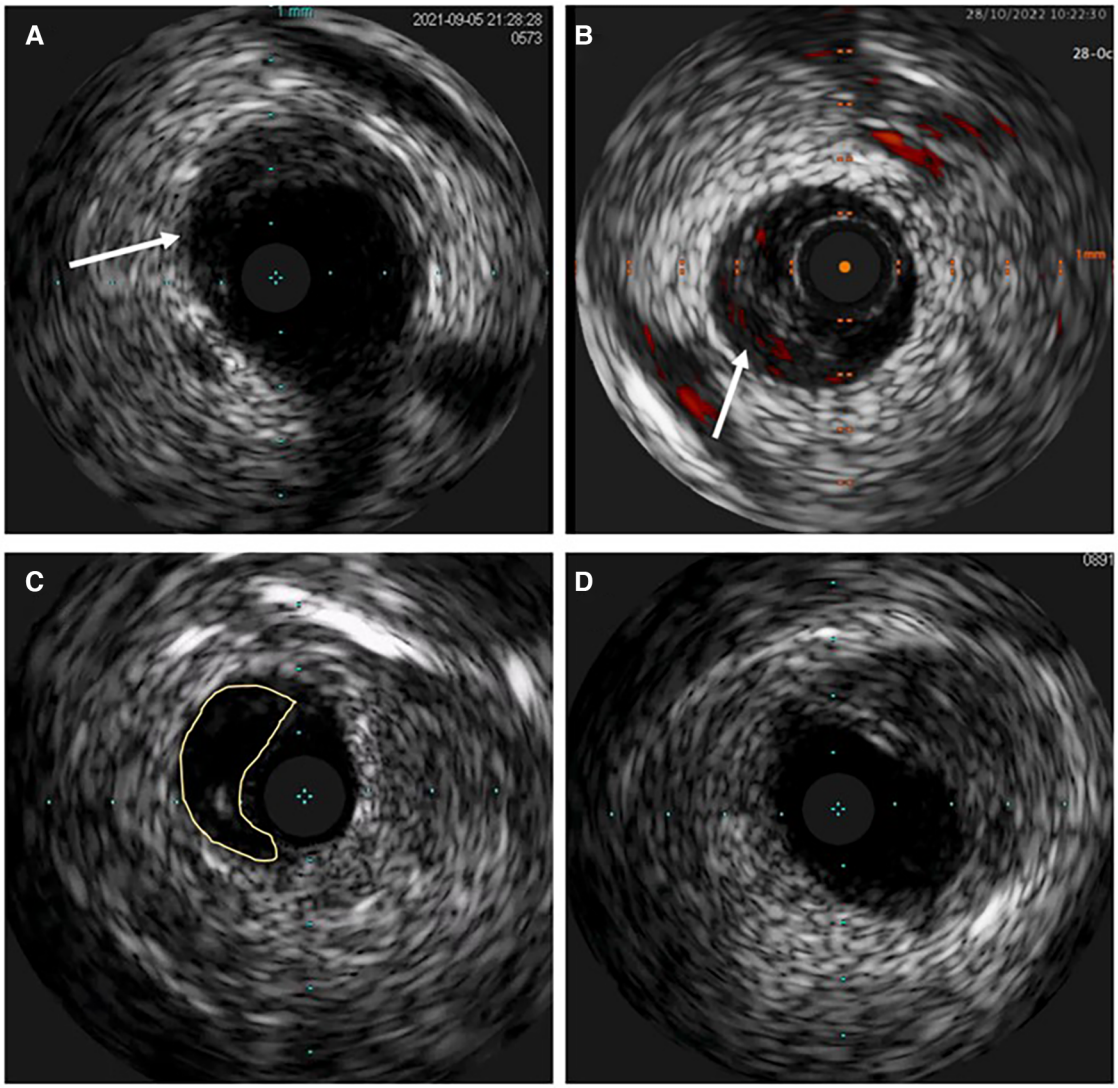


FIGURE 6
Intravascular ultrasound (IVUS) image of spontaneous coronary artery dissection (SCAD). (**A**) Intramural hematoma with the dissection entry (arrow). (**B**) ChromaFlow highlighting blood flow within intramural hematoma (IMH) with red color (arrow). (**C**) True and false lumen (yellow field) with the IVUS probe in the true lumen. (**D**) IMH in the left main resembles lipid-rich atheroma. Careful analysis of the entire pull-back length may be required in such cases.

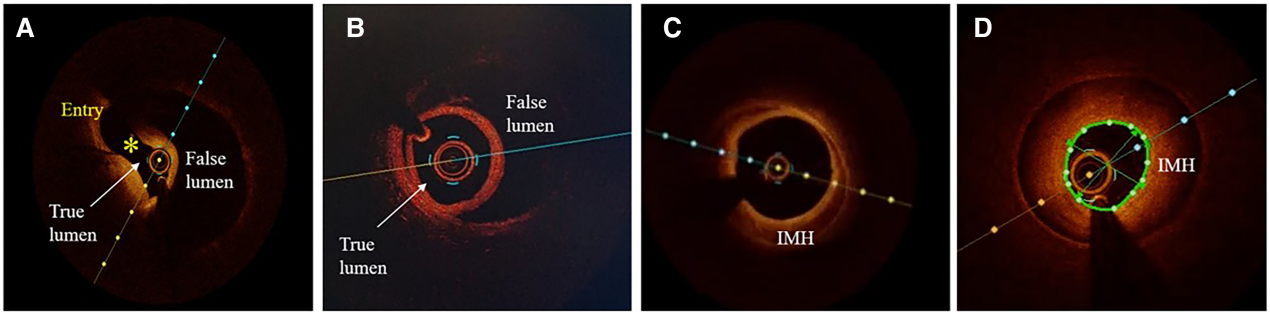


FIGURE 7
Optical coherence tomographic (OCT) imaging of SCAD. (**A**) A typical picture of the true and false lumen with visible dissection entry (asterisk). (**B**) True and false lumen without connection and with OCT probe situated within the true lumen. (**C**) IMH with incomplete dehiscence of the true lumen from the vessel wall. (**D**) Circumferential intramural hematoma (IMH) with complete dehiscence.

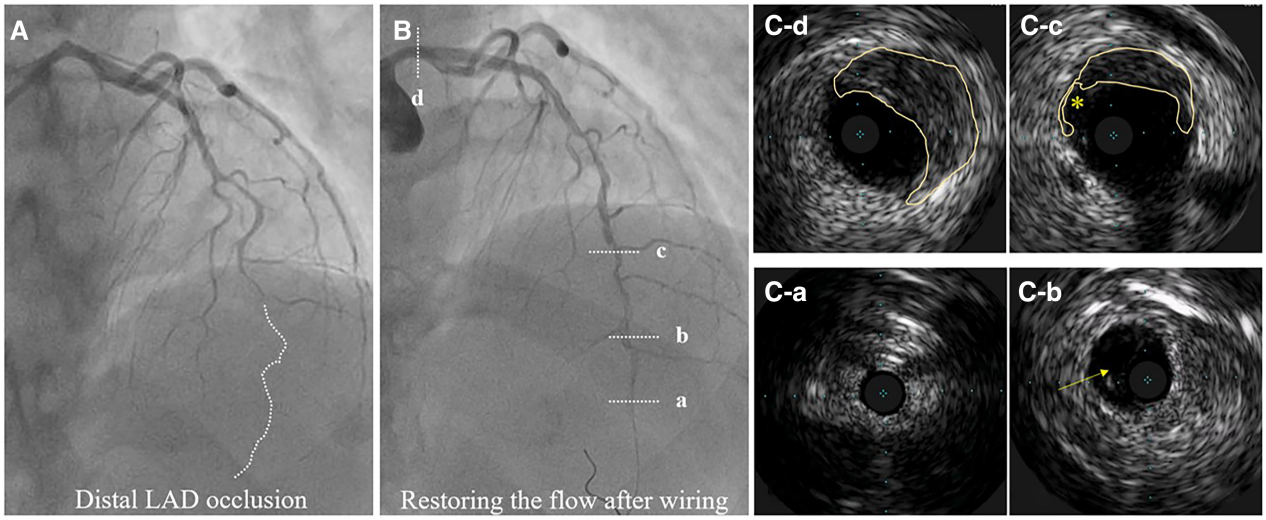


FIGURE 8
Hybrid SCAD diagnosed by IVUS. (**A**) Baseline angiography, dotted line depicts missing distal left anterior descending (LAD) artery. (**B**) flow restauration after wiring. (**C-a**) Distal, not diseased LAD. (**C-b**) Distal LAD with a visible true and false lumen. (**C-c**) IMH from 9 to 3 o'clock and dissection entry (*). (**C-d**) IMH in the left main (from 10 to 5 o'clock).

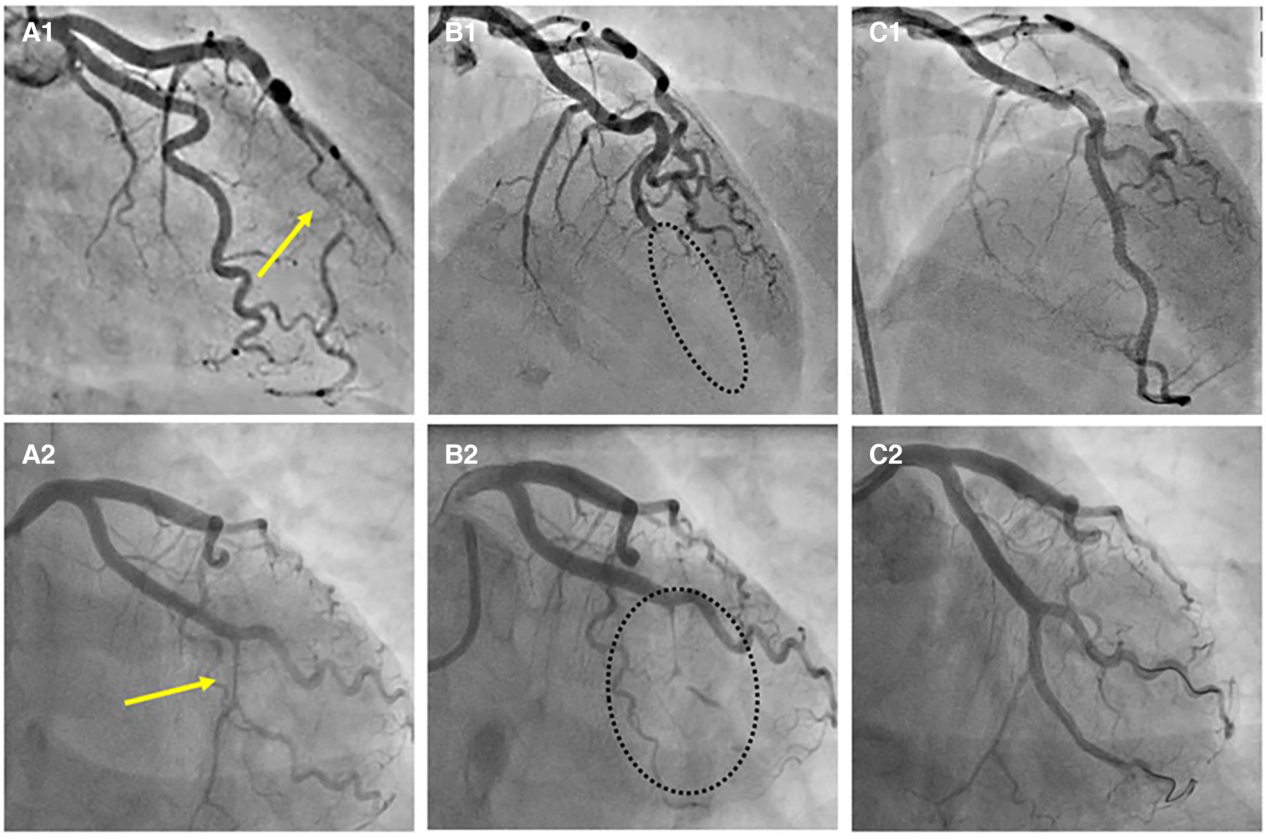


FIGURE 9
Progression of SCAD. (**A1**) SCAD Type 2a in distal left anterior descending (LAD) artery (arrow), referred for OMT. (**A2**) SCAD Type 2a in left circumflex (LCX) artery (arrow), referred for OMT. (**B1,B2**) Progression to SCAD Type 4 during watchful waiting strategy-dotted lines depict missing LAD (B1) and missing LCX (B2). (**C1, C2**) Final result after PCI.

Angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, mineralocorticoid receptor antagonists, and beta-blockers are recommended in SCAD patients with significant impairment of left ventricular systolic function according to heart failure guidelines (63). Due to the possible protective role of beta-blockers for SCAD recurrence, beta-blocker should be considered in all patients (3). The rationale for statin therapy in SCAD patients is unknown, and it is reserved for patients with preexisting dyslipidemia.

In hemodynamically unstable patients with ongoing ischaemia and impaired distal coronary flow, and when high-risk anatomic features (left-main involvement or multivessel SCAD) are anticipated, revascularization should be an option (5, 21). Additional risks might be encountered during PCI, from wiring the false lumen, inadequate stent sizing and expansion, iatrogenic dissection, hematoma propagation, side branch occlusion, and late stent malapposition after IMH resorption. Thus, intravascular imaging is highly endorsed to guide the procedure.

The main objective of PCI should be the restoration of blood flow mainly with plain old balloon angioplasty (POBA), preferably by a cutting balloon for hematoma fenestration and depressurizing the false lumen. If the decision to implant stent is undertaken, to avoid hematoma expansion, it is advisable to perform direct stenting, either with one longer stent or with a three-stent technique, covering distal and proximal dissections edges before stenting the intermediate segment (64). The use of bioresorbable stents may be beneficial by providing a temporary scaffolding of the vessel and avoiding late stent malapposition after IMH resorption (65).

Regarding revascularization options, PCI is recommended over coronary artery bypass grafting (CABG). The latter is reserved for PCI failure or when there is a substantial myocardium at risk (left main bifurcation involvement or multivessel SCAD) (21). In these circumstances, venous grafts are preferable, given the risk of graft failure due to the healing of the native coronary arteries and subsequent competitive flow.

Cardiogenic shock (CS) can complicate SCAD. The true prevalence of CS in SCAD patients is unknown (5, 13). However, Lobo et al. (17) reported that the prevalence of CS in SCAD presenting with STEMI is twice that of atherothrombotic STEMI (19% vs. 9%) and most often associated with left main dissection. An even higher prevalence of CS in SCAD is described in a systematic review of 120 pregnant women, with 24% presenting with cardiogenic shock and requiring mechanical circulatory support (MCS) and subsequent revascularization or heart transplantation (48). The utility of MCS in patients with SCAD is mainly based on several case reports documenting successful use of intra-aortic balloon pump (IABP), Impella, venoarterial extracorporeal membrane oxygenation (VA-ECMO), or left ventricular assist device (LVAD), either as a bridge to recovery or heart transplantation (48, 50, 66, 67).

Outcomes and follow-up

In SCAD survivors, long-term mortality is very low (**Table 1**), with a 10-year survival rate of 92% in the USA Mayo Clinic series (68) to 100% survival rate in Swiss series with a median follow-up of 4.5 years (27). However, the overall major adverse cardiac events (MACE) in these patients are common but with considerable variation between published series, ranging from 14.6% of 6-year MACE in the Italian series (24) to 47.4% of 10-year MACE in the US series (68). MACE is primarily driven by target vessel revascularization in PCI-treated SCAD and SCAD recurrence. The recurrence rate has been estimated to diverge (**Table 1**) from 2% in a 2-year follow-up (32) to 27% in a 5-year follow-up (21). Recurrent SCAD often involves new territory and may manifest as a different angiographic type than previously. The main contributors to SCAD recurrence are hypertension (28), and severe coronary tortuosity (10), while beta-blocker use may be protective (28).

Given the known risk for catheter-induced iatrogenic dissection in SCAD patients (59), routine angiographic follow-up is not recommended. For that purpose, CCTA, although with limited potential in the diagnostic algorithm (69), can be a valuable option to confirm SCAD healing, particularly in SCAD type 1 (7, 8). However, further data is needed before CCTA can be recommended for SCAD follow-up.

Conclusion

Spontaneous coronary artery dissection is a common cause of myocardial infarction in young adults, particularly women. Distinct from atherosclerotic ACS by pathophysiology, with several non-traditional risk factors and associated conditions that can increase the likelihood of SCAD, the final diagnosis is made by coronary angiography with or without intravascular imaging techniques. However, apart from well-known SCAD angiographic patterns, occasionally, it is challenging to distinguish it from atherosclerotic plaque rupture or erosion, coronary vasospasm, spontaneous recanalized thrombus, embolism or iatrogenic dissection. Therefore, intravascular imaging is advisable to confirm SCAD-specific features such as intramural hematoma or intimal tear with a clear recognition of true and false lumen. Finally, timely and accurate diagnosis is essential as there are differences in the acute and long-term management of SCAD and other causes of ACS, with the recommendation for conservative management of SCAD whenever possible.

Author contributions

MK: Conceptualization, Writing – original draft, Investigation, Writing – review & editing, Supervision. MJ: Writing – original draft, Writing – review & editing. AM: Writing – review & editing. MP: Writing – review & editing. MC: Data curation, Writing – review & editing. MB: Investigation, Writing – review & editing. AI: Supervision, Writing – review & editing. IS: Investigation, Writing – review & editing. ST: Conceptualization, Writing – review & editing. DD: Data curation, Writing—review & editing. BC: Data curation, Writing – review & editing. NK: Data curation, Writing – review & editing. ND: Investigation, Writing – review & editing. SA: Supervision, Writing – review &

editing. DS: Writing – review & editing. VK: Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Adlam D, Tweet MS, Gulati R, Kotecha D, Rao P, Moss AJ, et al. Spontaneous coronary artery dissection: pitfalls of angiographic diagnosis and an approach to ambiguous cases. *JACC Cardiovasc Interv*. (2021) 14(16):1743–56. doi: 10.1016/j.jcin.2021.06.027

2. Khiatah B, Jazayeri S, Yamamoto N, Burt T, Frugoli A, Brooks DL. Cardiovascular disease in women: a review of spontaneous coronary artery dissection. *Medicine (Baltimore)*. (2022) 101(38):e30433. doi: 10.1097/MD.0000000000030433

3. Lewey J, El Hajj SC, Hayes SN. Spontaneous coronary artery dissection: new insights into this not-so-rare condition. *Annu Rev Med*. (2022) 73:339–54. doi: 10.1146/annurev-med-052819-023826

4. Pretty HC. Dissecting aneurysm of coronary artery in a woman aged 42. *British Medical J*. (1931) 1:667. doi: 10.1136/bmj.1.3667.667

5. Adlam D, Alfonso F, Maas A, Vrints C, Committee W. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. (2018) 39 (36):3353–68. doi: 10.1093/eurheartj/ehy080

6. Hayes SN, Tweet MS, Adlam D, Kim ESH, Gulati R, Price JE, et al. Spontaneous coronary artery dissection: JACC state-of-the-art review. *J Am Coll Cardiol*. (2020) 76 (8):961–84. doi: 10.1016/j.jacc.2020.05.084

7. Pergola V, Continisio S, Mantovani F, Motta R, Mattesi G, Marrazzo G, et al. Spontaneous coronary artery dissection: the emerging role of coronary computed tomography. *Eur Heart J Cardiovasc Imaging*. (2023) 24(7):839–50. doi: 10.1093/ehjci/jead060

8. Bin Saeedan M, Ramchand J, Bolen M. Role of computed tomography angiography in setting of spontaneous coronary artery dissection. *Curr Probl Diagn Radiol*. (2021) 50(4):532–9. doi: 10.1067/j.cpradiol.2020.07.010

9. Russo V, Marrozzini C, Zompatori M. Spontaneous coronary artery dissection: role of coronary CT angiography. *Heart Br Card Soc*. (2013) 99(9):672–3. doi: 10.1136/heartjnl-2012-303215

10. Eleid MF, Guddeti RR, Tweet MS, Lerman A, Singh M, Best PJ, et al. Coronary artery tortuosity in spontaneous coronary artery dissection: angiographic characteristics and clinical implications. *Circ Cardiovasc Interv*. (2014) 7(5):656–62. doi: 10.1161/CIRCINTERVENTIONS.114.001676

11. Morrone D, Gentile F, Aimo A, Cameli M, Barison A, Picoi ME, et al. Perspectives in noninvasive imaging for chronic coronary syndromes. *Int J Cardiol*. (2022) 365:19–29. doi: 10.1016/j.ijcard.2022.07.038

12. Bergamaschi L, Foà A, Paolisso P, Renzulli M, Angeli F, Fabrizio M, et al. Prognostic role of early cardiac magnetic resonance in myocardial infarction with nonobstructive coronary arteries. *JACC Cardiovasc Imaging*. (2023):S1936–878X.(23)00242-5. doi: 10.1016/j.jcmg.2023.05.016

13. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation*. (2018) 137(19): e523–57. doi: 10.1161/CIR.0000000000000564

14. Tweet MS, Eleid MF, Best PJM, Lennon RJ, Lerman A, Rihal CS, et al. Spontaneous coronary artery dissection: revascularization versus conservative therapy. *Circ Cardiovasc Interv*. (2014) 7(6):777–86. doi: 10.1161/CIRCINTERVENTIONS.114.001659

15. Alfonso F, Paulo M, Lennie V, Dutary J, Bernardo E, Jiménez-Quevedo P, et al. Spontaneous coronary artery dissection: long-term follow-up of a large series of patients prospectively managed with a "conservative" therapeutic strategy. *JACC Cardiovasc Interv*. (2012) 5(10):1062–70. doi: 10.1016/j.jcin.2012.06.014

16. Nakashima T, Noguchi T, Haruta S, Yamamoto Y, Oshima S, Nakao K, et al. Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: a report from the angina pectoris-myocardial infarction multicenter investigators in Japan. *Int J Cardiol*. (2016) 207:341–8. doi: 10.1016/j.ijcard.2016.01.188

17. Lobo AS, Cantu SM, Sharkey SW, Grey EZ, Storey K, Witt D, et al. Revascularization in patients with spontaneous coronary artery dissection and ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. (2019) 74 (10):1290–300. doi: 10.1016/j.jacc.2019.06.065

18. Smilowitz NR, Gupta N, Guo Y, Zhong J, Weinberg CR, Reynolds HR, et al. Acute myocardial infarction during pregnancy and the puerperium in the United States. *Mayo Clin Proc*. (2018) 93(10):1404–14. doi: 10.1016/j.mayocp.2018.04.019

19. Kim ESH. Spontaneous coronary-artery dissection. *N Engl J Med*. (2020) 383 (24):2358–70. doi: 10.1056/NEJMra2001524

20. Lebrun S, Bond RM. Spontaneous coronary artery dissection (SCAD): the underdiagnosed cardiac condition that plagues women. *Trends Cardiovasc Med*. (2018) 28(5):340–5. doi: 10.1016/j.tcm.2017.12.004

21. Saw J, Mancini GBJ, Humphries KH. Contemporary review on spontaneous coronary artery dissection. *J Am Coll Cardiol*. (2016) 68(3):297–312. doi: 10.1016/j.jacc.2016.05.034

22. Yip A, Saw J. Spontaneous coronary artery dissection-A review. *Cardiovasc Diagn Ther*. (2015) 5(1):37–48. doi: 10.3978/j.issn.2223-3652.2015.01.08

23. Waterbury TM, Tweet MS, Hayes SN, Eleid MF, Bell MR, Lerman A, et al. Early natural history of spontaneous coronary artery dissection. *Circ Cardiovasc Interv*. (2018) 11(9):e006772. doi: 10.1161/CIRCINTERVENTIONS.118.006772

24. Lettieri C, Zavalloni D, Rossini R, Morici N, Ettori F, Leonzi O, et al. Management and long-term prognosis of spontaneous coronary artery dissection. *Am J Cardiol*. (2015) 116(1):66–73. doi: 10.1016/j.amjcard.2015.03.039

25. McGrath-Cadell L, McKenzie P, Emmanuel S, Muller DWM, Graham RM, Holloway CJ. Outcomes of patients with spontaneous coronary artery dissection. *Open Heart*. (2016) 3(2):e000491. doi: 10.1136/openhrt-2016-000491

26. Faden MS, Bottega N, Benjamin A, Brown RN. A nationwide evaluation of spontaneous coronary artery dissection in pregnancy and the puerperium. *Heart Br Card Soc*. (2016) 102(24):1974–9. doi: 10.1136/heartjnl-2016-309403

27. Rogowski S, Maeder MT, Weilenmann D, Haager PK, Ammann P, Rohner F, et al. Spontaneous coronary artery dissection: angiographic follow-up and long-term clinical outcome in a predominantly medically treated population. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. (2017) 89(1):59–68. doi: 10.1002/ccd.26383

28. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol*. (2017) 70(9):1148–58. doi: 10.1016/j.jacc.2017.06.053

29. Clare R, Duan L, Phan D, Moore N, Jorgensen M, Ichiuji A, et al. Characteristics and clinical outcomes of patients with spontaneous coronary artery dissection. *J Am Heart Assoc*. (2019) 8(10):e012570. doi: 10.1161/JAHA.119.012570

30. Mori R, Macaya F, Giacobbe F, Salinas P, Pavani M, Boi A, et al. Clinical outcomes by angiographic type of spontaneous coronary artery dissection. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol*. (2021) 17(6):516–24. doi: 10.4244/EIJ-D-20-01275

31. Saw J, Starovoytov A, Aymong E, Inohara T, Alfadhel M, McAlister C, et al. Canadian Spontaneous coronary artery dissection cohort study: 3-year outcomes. *J Am Coll Cardiol*. (2022) 80(17):1585–97. doi: 10.1016/j.jacc.2022.08.759

32. García-Guimaraes M, Bastante T, Macaya F, Roura G, Sanz R, Barahona Alvarado JC, et al. Spontaneous coronary artery dissection in Spain: clinical and angiographic characteristics, management, and in-hospital events. *Rev Espanola Cardiol Engl Ed*. 2021;74(1):15–23. doi: 10.1016/j.recesp.2020.02.008

33. Jensen CW, Kang L, Moya-Mendez ME, Rhodin KE, Vekstein AM, Schuyler Jones W, et al. Initial management strategy and long-term outcomes in 186 cases of spontaneous coronary artery dissection. *Semin Thorac Cardiovasc Surg*. (2023): S1043-0679(23)00088-6. doi: 10.1053/j.semtcvs.2023.05.001

34. Fahmy P, Prakash R, Starovoytov A, Boone R, Saw J. Pre-Disposing and precipitating factors in men with spontaneous coronary artery dissection. *JACC Cardiovasc Interv*. (2016) 9(8):866–8. doi: 10.1016/j.jcin.2016.02.024

35. Pizzi C, Santarella L, Costa MG, Manfrini O, Flacco ME, Capasso L, et al. Pathophysiological mechanisms linking depression and atherosclerosis: an overview. *J Biol Regul Homeost Agents*. (2012) 26(4):775–82.

36. Tweet MS, Miller VM, Hayes SN. The evidence on estrogen. Progesterone, and spontaneous coronary artery dissection. *JAMA Cardiol*. (2019) 4(5):403–4. doi: 10.1001/jamacardio.2019.0774

37. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, et al. Canadian Spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J*. (2019) 40(15):1188–97. doi: 10.1093/eurheartj/ehz007

38. Kok SN, Hayes SN, Cutrer FM, Raphael CE, Gulati R, Best PJM, et al. Prevalence and clinical factors of migraine in patients with spontaneous coronary artery dissection. *J Am Heart Assoc*. (2018) 7(24):e010140. doi: 10.1161/JAHA.118.010140

39. Miller VM, Duckles SP. Vascular actions of estrogens: functional implications. *Pharmacol Rev*. (2008) 60(2):210–41. doi: 10.1124/pr.107.08002

40. Prasad M, Tweet MS, Hayes SN, Leng S, Liang JJ, Eleid MF, et al. Prevalence of extracoronary vascular abnormalities and fibromuscular dysplasia in patients with spontaneous coronary artery dissection. *Am J Cardiol*. (2015) 115(12):1672–7. doi: 10.1016/j.amjcard.2015.03.011

41. Carss KJ, Baranowska AA, Armisen J, Webb TR, Hamby SE, Premawardhana D, et al. Spontaneous coronary artery dissection: insights on rare genetic variation from genome sequencing. *Circ Genomic Precis Med*. (2020) 13(6):e003030. doi: 10.1161/CIRCGEN.120.003030

42. Mawet J, Kurth T, Ayata C. Migraine and stroke: in search of shared mechanisms. *Cephalalgia Int J Headache*. (2015) 35(2):165–81. doi: 10.1177/0333102414550106

43. Metso TM, Tatlisumak T, Debette S, Dallongeville J, Engelter ST, Lyrer PA, et al. Migraine in cervical artery dissection and ischemic stroke patients. *Neurology*. (2012) 78(16):1221–8. doi: 10.1212/WNL.0b013e318251595f

44. Smyth A, O'Donnell M, Lamelas P, Teo K, Rangarajan S, Yusuf S, et al. Physical activity and anger or emotional upset as triggers of acute myocardial infarction: the INTERHEART study. *Circulation*. (2016) 134(15):1059–67. doi: 10.1161/CIRCULATIONAHA.116.023142

45. Y-Hassan S, Böhm F. The causal link between spontaneous coronary artery dissection and takotsubo syndrome: a case presented with both conditions. *Int J Cardiol*. (2016) 203:828–31. doi: 10.1016/j.ijcard.2015.11.047

46. Y-Hassan S, Themudo R, Maret E. Spontaneous coronary artery dissection and takotsubo syndrome: the chicken or the egg causality dilemma. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. (2017) 89(7):1215–8. doi: 10.1002/ccd.26956

47. Luong C, Starovoytov A, Heydari M, Sedlak T, Aymong E, Saw J. Clinical presentation of patients with spontaneous coronary artery dissection. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. (2017) 89(7):1149–54. doi: 10.1002/ccd.26977

48. Havakuk O, Goland S, Mehra A, Elkayam U. Pregnancy and the risk of spontaneous coronary artery dissection: an analysis of 120 contemporary cases. *Circ Cardiovasc Interv*. (2017) 10(3):e004941. doi: 10.1161/CIRCINTERVENTIONS.117.004941

49. Phan D, Clare R, Duan L, Kim C, Moore N, Lee MS. Characteristics and outcomes of patients with spontaneous coronary artery dissection who suffered sudden cardiac arrest. *J Interv Card Electrophysiol Int J Arrhythm Pacing*. (2021) 60(1):77–83. doi: 10.1007/s10840-019-00695-9

50. Ya'Qoub L, Alqarqaz M, Cowger J, Nemeh H, Basir MB, Alaswad K, et al. Cardiogenic shock in a young woman with SCAD: the importance of early access to VA-ECMO in the community. *Cardiovasc Revasc Med*. (2023):S1553-8389(23)00669-3. doi: 10.1016/j.carrev.2023.06.023

51. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best PJM. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol*. (2017) 70(4):426–35. doi: 10.1016/j.jacc.2017.05.055

52. Motreff P, Malcles G, Combaret N, Barber-Chamoux N, Bouajila S, Pereira B, et al. How and when to suspect spontaneous coronary artery dissection: novel insights from a single-centre series on prevalence and angiographic appearance. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol*. (2017) 12(18):e2236–43. doi: 10.4244/EIJ-D-16-00187

53. Saw J. Coronary angiogram classification of spontaneous coronary artery dissection. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. (2014) 84(7):1115–22. doi: 10.1002/ccd.25293

54. Saw J, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv*. (2014) 7(5):645–55. doi: 10.1161/CIRCINTERVENTIONS.114.001760

55. Al-Hussaini A, Adlam D. Spontaneous coronary artery dissection. *Heart Br Card Soc*. (2017) 103(13):1043–51. doi: 10.1136/heartjnl-2016-310320

56. Souteyrand G, Valladier M, Amabile N, Derimay F, Harbaoui B, Leddet P, et al. Diagnosis and management of spontaneously recanalized coronary thrombus guided by optical coherence tomography—lessons from the French "Lotus root" registry. *Circ J Off J Jpn Circ Soc*. (2018) 82(3):783–90. doi: 10.1253/circj.CJ-17-0810

57. Cankovic M, Drljevic Todic V, Pantic T, Kovacevic M, Ivanovic V, Petrovic M. Spontaneous recanalized coronary thrombus as an unexpected finding on coronary angiography. *Acta med croatica*. (2020) 74:375–8.

58. Del Val D, Bastante T, Rivero F, Cuesta J, Martinez-Avial M, Alfonso F. "Lotus root": a novel optical coherence tomography imaging pattern in spontaneous coronary artery dissection. *EuroIntervention J Eur Collab Work Group Interv Cardiol Eur Soc Cardiol*. (2023) 18(17):1458–9. doi: 10.4244/EIJ-D-22-00775

59. Prakash R, Starovoytov A, Heydari M, Mancini GBJ, Saw J. Catheter-Induced iatrogenic coronary artery dissection in patients with spontaneous coronary artery dissection. *JACC Cardiovasc Interv*. (2016) 9(17):1851–3. doi: 10.1016/j.jcin.2016.06.026

60. Yock PG, Linker DT, Angelsen BA. Two-dimensional intravascular ultrasound: technical development and initial clinical experience. *J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr*. (1989) 2(4):296–304. doi: 10.1016/S0894-7317(89)80090-2

61. Alfonso F, Paulo M, Gonzalo N, Dutary J, Jimenez-Quevedo P, Lennie V, et al. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. *J Am Coll Cardiol*. (2012) 59(12):1073–9. doi: 10.1016/j.jacc.2011.08.082

62. Jackson R, Al-Hussaini A, Joseph S, van Soest G, Wood A, Macaya F, et al. Spontaneous coronary artery dissection: pathophysiological insights from optical coherence tomography. *JACC Cardiovasc Imaging*. (2019) 12(12):2475–88. doi: 10.1016/j.jcmg.2019.01.015

63. M TA, M M, A M, G RS, B A, B M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. (2021) 42(36):3599–726. doi: 10.1093/eurheartj/ehab368

64. Krittanawong C, Kumar A, Johnson KW, Luo Y, Yue B, Wang Z, et al. Conditions and factors associated with spontaneous coronary artery dissection (from a national population-based cohort study). *Am J Cardiol*. (2019) 123(2):249–53. doi: 10.1016/j.amjcard.2018.10.012

65. Cockburn J, Yan W, Bhindi R, Hansen P. Spontaneous coronary artery dissection treated with bioresorbable vascular scaffolds guided by optical coherence tomography. *Can J Cardiol*. 2014 Nov;30(11):1461.e1–3. doi: 10.1016/j.cjca.2014.06.025

66. Sharma S, Polak S, George Z, LeDoux J, Sohn R, Stys A, et al. Management of spontaneous coronary artery dissection complicated by cardiogenic shock using mechanical circulatory support with the impella device. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv*. (2021) 97(1):74–7. doi: 10.1002/ccd.28677

67. Jorge-Pérez P, García-González MJ, Ávalos-Pinto RM, G-Cosio-Carmena MD, Renes-Carreño E, Delgado JF, et al. Spontaneous coronary dissection and cardiogenic shock requiring mechanical circulatory support in a non-transplant center. *Int J Cardiol*. (2016) 221:629–30. doi: 10.1016/j.ijcard.2016.07.015

68. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation*. (2012) 126(5):579–88. doi: 10.1161/CIRCULATIONAHA.112.105718

69. Eleid MF, Tweet MS, Young PM, Williamson E, Hayes SN, Gulati R. Spontaneous coronary artery dissection: challenges of coronary computed tomography angiography. *Eur Heart J Acute Cardiovasc Care*. (2018 Oct) 7(7):609–13. doi: 10.1177/2048872616687098

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 19 December 2023
DOI 10.3389/fcvm.2023.1273301

OPEN ACCESS

EDITED BY
Tommaso Gori,
University Medical Centre, Johannes Gutenberg University Mainz,

REVIEWED BY
Luca Bergamaschi,
University of Bologna, Italy
Alessandra Repetto,
San Matteo Hospital Foundation (IRCCS), Italy

*CORRESPONDENCE
Dragana Stanojevic
draganastanojevic1@gmail.com

RECEIVED 05 August 2023
ACCEPTED 29 November 2023
PUBLISHED 19 December 2023

CITATION
Stanojevic D, Apostolovic S, Kostic T, Mitov V, Kutlesic-Kurtovic D, Kovacevic M, Stanojevic J, Milutinovic S and Beleslin B (2023) A review of the risk and precipitating factors for spontaneous coronary artery dissection. Front. Cardiovasc. Med. 10:1273301. doi: 10.3389/fcvm.2023.1273301

A review of the risk and precipitating factors for spontaneous coronary artery dissection

Dragana Stanojevic[1]*, Svetlana Apostolovic[1,2], Tomislav Kostic[1,2], Vladimir Mitov[3], Dusanka Kutlesic-Kurtovic[1], Mila Kovacevic[4,5], Jelena Stanojevic[2], Stefan Milutinovic[6] and Branko Beleslin[7,8]

[1]Clinic for Cardiology, University Clinical Center Nis, Nis, Serbia, [2]Internal Medicine Department, Medical Faculty University of Nis, Nis, Serbia, [3]Department for Cardiovascular Diseases, Health Center Zajecar, Zajecar, Serbia, [4]Clinic for Cardiology, Institute for Cardiovascular Diseases Vojvodina, Novi Sad, Serbia, [5]Internal Medicine Department, Medical Faculty University of Novi Sad, Novi Sad, Serbia, [6]Internal Medicine Residency Program, Florida State University College of Medicine, Cape Coral, FL, United States, [7]Clinic for Cardiology, University Clinical Centre Serbia, Belgrade, Serbia, [8]Internal Medicine Department, Medical Faculty Belgrade, Belgrade, Serbia

Introduction: Spontaneous coronary artery dissection (SCAD) accounts for 1%–4% of cases of acute coronary syndrome (ACS). SCAD is caused by separation occurring within or between any of the three tunics of the coronary artery wall. This leads to intramural hematoma and/or formation of false lumen in the artery, which leads to ischemic changes or infarction of the myocardium. The incidence of SCAD is higher in women than in men, with a ratio of approximately 9:1. It is estimated that SCAD is responsible for 35% of ACS cases in women under the age of 60. The high frequency is particularly observed during pregnancy and in the peripartum period (first week). Traditional risk factors are rare in patients with SCAD, except for hypertension. Patients diagnosed with SCAD have different combinations of risk factors compared with patients who have atherosclerotic changes in their coronary arteries. We presented the most common so-called "non-traditional" risk factors associated with SCAD patients.

Risk factors and precipitating disorders which are associated with SCAD: In the literature, there are few diseases frequently associated with SCAD, and they are identified as predisposing factors. The predominant cause is fibromuscular dysplasia, followed by inherited connective tissue disorders, systemic inflammatory diseases, pregnancy, use of sex hormones or steroids, use of cocaine or amphetamines, thyroid disorders, migraine, and tinnitus. In recent years, the genetic predisposition for SCAD is also recognized as a predisposing factor. The precipitating factors are also different in women (emotional stress) compared with those in men (physical stress). Women experiencing SCAD frequently describe symptoms of anxiety and depression. These conditions could increase shear stress on the arterial wall and dissection of the coronary artery wall. Despite the advancement of SCAD, we can find significant differences in the clinical presentation between women and men.

Conclusion: When evaluating patients with chest pain or other ACS symptoms who have a low cardiovascular risk, particularly female patients, it is important to consider the possibility of ACS due to SCAD, particularly in conditions often associated with SCAD. This will increase the recognition of SCAD and the timely treatment of affected patients.

KEYWORDS

spontaneous coronary artery dissection, non-traditional risk factors, fibromuscular dysplasia, pregnancy, emotional stress

1. Introduction

Approximately 1%–4% of patients diagnosed with acute coronary syndrome (ACS) are predicted to have spontaneous coronary artery dissection (SCAD), which challenges the perception that SCAD is a rare disease. SCAD is characterized by separation occurring within or between any of the three tunics of the coronary artery wall which is not caused by trauma. Thus, the formation of an intramural hematoma and/or false lumen occurs, resulting in myocardial infarction (MI) in the form of either STEMI (up to 37%) or NSTEMI (53%–59%). In addition, it leads to sudden cardiac death in 3.6%–10% of cases (1, 2).

SCAD is not associated with coronary atherosclerosis and lipid accumulation. The development of SCAD is explained with two theories. The first theory explains that the formation of intramural hematoma is caused by the tearing of the innermost tunica of the coronary artery, while the second theory is focused on the outer layer and the rupture of its blood vessels, resulting in similar consequences (3, 4).

After careful examination of coronary angiograms, the frequency of SCAD was reported to be between 23% and 36% in women under the age of 60. This high prevalence indicates that this condition is frequently misdiagnosed (2, 5). During pregnancy or the peripartum period, ACS is caused by SCAD in up to 43% of cases (1, 6, 7).

SCAD predominantly affects the left anterior descending artery, in approximately 50% of cases, with the left circumflex and right coronary arteries being affected subsequently. Over 90% of patients experience dissection in the mid and distal segments of epicardial arteries, while 13% of cases involve the left main artery, and approximately 5%–10% of cases affect two or more coronary arteries (4).

In most prospective registries, SCAD is most frequently diagnosed in Caucasians and predominantly in women compared with men (9:1). In certain observational cohorts, there is a deviation from the typical trend, with men being more frequently diagnosed with SCAD than previously reported. In one study with more than 30,000 patients with ACS, even 1.2% of patients were found to have a diagnosis of SCAD, with males accounting for 35.7% of these cases (1, 8). Published literature indicates that men with SCAD were significantly younger than women (approximately 48 vs. 52 years).

The pathophysiology of SCAD is remains uncertain; however, it is possibly that a combination of risk factors with predisposing conditions and precipitating factors facilitate its development. A few risk factors such as female sex, pregnancy, and fibromuscular dysplasia (FMD) are strongly linked with SCAD in multiple studies. The link between SCAD and other reported associated conditions or risk factors has not been established, as previously mentioned (**Figure 1**) (10).

SCAD is often referred to as disease in patients without the traditional risk factors for coronary artery disease (11). However, traditional risk factors such as hypertension, hyperlipidemia, smoking, and obesity are present in those patients. Further, hypertension is found in almost similar percentage of patients with SCAD compared with age-matched population. The presence of traditional risk factors does not exclude the diagnosis of SCAD in young patients with ACS (12).

SCAD-related risk factors such as migraine and FMD should be determined with the goal of precise and prompt diagnosis, adequate therapy, and prognosis in this potentially fatal and recurrent disease. In addition, it is crucial to recognize the preceding precipitants that trigger SCAD, such as physical or emotional distress, which are more prevalent in SCAD than in ACS caused by atherosclerosis, for comprehensive management. Recently published studies have shown that emotional stressors are more prevalent in SCAD than in MI caused by atherosclerosis (56% vs. 17%), and similarly, physical exertion are more prevalent in SCAD than in MI caused by atherosclerosis (24% vs. 14%) (3).

We present the review of the prevalent non-traditional risk factors associated with SCAD, which are important for diagnosis, treatment, individual rehabilitation programs, and ultimately, patient prognosis.

1.1. Female sex and pregnancy

The highest percentage of SCAD patients (approximately 90%) are perimenopausal women. The predominance of females among SCAD patients and its high prevalence in pregnancy suggest that sex hormones play a significant role in the pathophysiology of this condition. The precise mechanisms of this pathophysiology association are still undetermined. Female sex hormones have an impact on arterial connective tissue and microvasculature. The obtained results suggest that the risk factors for SCAD in pregnancy (P-SCAD) include having more than one pregnancy, using sex hormones for *in vitro* fertilization (IVF), and having pre-eclampsia (6, 10).

Most events are reported during the last trimester and during the first week of the postpartum period. SCAD may occur even in the late postpartum (6–12 months) period, and it is linked with breastfeeding (10). A comprehensive study conducted in Canada between 2008 and 2012 revealed a higher incidence of P-SCAD compared with the data from prior studies (1.8 cases per 100,000 pregnancies). In the same study, P-SCAD patients exhibited worse prognosis than SCAD females who were not pregnant (NP-SCAD) having more frequently STEMI (64%), cardiogenic shock (24%), cardiac arrest (14%), and death (4.5%). P-SCAD patients exhibited a higher incidence of proximal coronary artery dissection and a significantly decreased left ventricle ejection fraction (LVEF) of ≤35%. This data regarding the poor prognosis in P-SCAD compared with NP-SCAD patients was confirmed in another American study (10).

Patients with P-SCAD compared with NP-SCAD had a higher prevalence of black ethnicity, older, with a history of arterial hypertension and hyperlipidemia, more often had depression, migraines, and more frequently were treated for infertility (1).

The hormonal and hemodynamic changes that occur during pregnancy, along with the increased shear stress on the coronary arteries, may contribute in developing SCAD. Within the initial 6 weeks of pregnancy, hemodynamics starts to change, including an

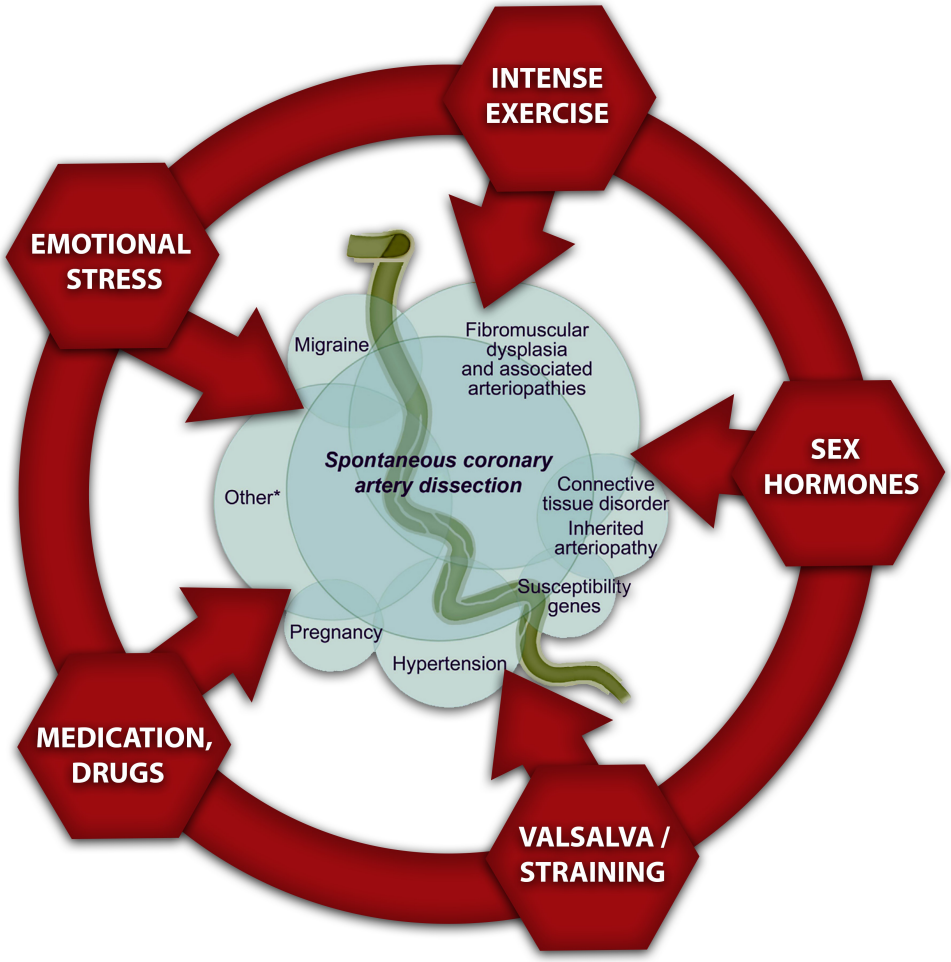


FIGURE 1
Risk and precipitating factors for SCAD.

increase in blood volume and in red blood cell mass while systemic vascular resistance is decreasing, and consequently, the cardiac output is higher. These changes are expected, but they increase the oxygen demands of the myocardium and could lead to developing SCAD. As previously stated, the highest incidence of P-SCAD was observed in the first month after childbirth, with the peak of incidence observed within the first postpartum week. During this period, there is another rapid increase in cardiac output due to the fast return of blood from the contracted uterus. Progesterone and estrogen have the highest levels during this period, which could be important since the endothelium has the sex hormone receptors. Estrogen induces the release of nitric oxide, resulting in vasodilatation, but it also influences the function of matrix metalloproteinases, which degrades the components of the artery wall and therefore contributes to SCAD (2–6). SCAD was also reported during lactation when oxytocin is released, which affects vasculature. Importantly, one of the metabolic products of oxytocin degradation is cardiotoxic and is found to be responsible for the occurrence of peripartum cardiomyopathy. This could also be important for the pathophysiology of SCAD (2–6).

1.2. Exogenous hormones

The use of oral estrogen and progesterone were linked to an increased risk of developing SCAD in few reports (one single-center study with case reports) (13). Estrogen replacement therapy has known effects on coagulation, microcirculation, increased release of reactive oxygen species, and triggering arrhythmias, all of which may potentially be associated with SCAD (13). However, in a study conducted by Saw et al. (14) on a group of 168 females with SCAD, no association was found between the active use of oral combined hormone therapy and the incidence of SCAD.

There is limited data available regarding SCAD occurrence after *in vitro* fertilization. In the United States, 9% of patients with P-SCAD underwent IVF. Women with P-SCAD more frequently underwent IVF treatment compared with women in childbearing age in the US population (28% vs. 12%) (15, 16). In this process, patients are administered gonadotropin therapy together with selective estrogen modulators and aromatase inhibitors to stimulate the production of follicles that secrete

high levels of estrogen and progesterone. As previously mentioned, these hormones could cause weakening and vascular wall rupture. Clomiphene is the most frequently used selective estrogen receptor modulator in IVF, and previously, it has been linked with different pathological conditions such as MI and potentially with SCAD (16).

The role of estrogen and progesterone levels or their fluctuations in SCAD occurrence is unclear. A limited number of studies have explored SCAD development during menstruation, hormone replacement therapy, and in women undergoing or having undergone IVF treatment (17).

One hypotheses explaining the gender difference in SCAD is the various responses to androgens in the cardiovascular system and other organs. The X chromosome contains genes responsible for the expression of androgen receptors. In females, the different response to androgens is the result of autosomal mosaicism. It is known that estrogens are synthetized from androgen precursors, catalyzed by aromatase. Furthermore, women frequently exhibit specific coronary anatomy characterized by tortuous coronary vessels and a predisposition to microvascular dysfunction as a consequence of increased metalloprotease activity induced by estrogens (13).

1.3. Systemic arteriopathies

Connective tissue disorders, such as Marfan syndrome, Ehlers–Danlos syndrome type 4, and Loeys–Dietz syndromes, as well as polycystic kidney disease, are found in <5% of patients with SCAD (18, 19). The diagnosis of these conditions is important as it can guide familial screening and careful follow-up of affected patients (19).

Patients with SCAD in whom arterial imaging for extra-coronary vascular abnormalities was performed frequently exhibited fibromuscular dysplasia (18). The DISCO study is the first European multicenter analysis of SCAD patients and one of the largest studies in the world. The prevalence of FMD in this large cohort of SCAD patients was found to be 45% (20).

Marfan syndrome is caused by mutations in the fibrillin-1 gene (*FBN1*), and, among other abnormalities, patients with this syndrome exhibit dilatation of the aortic sinus with an increased risk of type A aortic dissection. There is a limited number of case reports in the literature regarding SCAD in patients with Marfan syndrome, and these reports suggest that the association between these entities lies in the structural changes in the connective tissue of the artery wall, which predispose to vessel dissection (2, 21).

In vascular Ehlers–Danlos syndrome, mainly middle-sized muscular arteries are affected, namely, mutations in the alpha 1 gene (*COL3A1*) are the cause of this syndrome. Collagen type III synthesis is disrupted, and consequently, patients are at risk for vascular rupture. SCAD has been reported to be associated with this syndrome in a limited number of case reports (2, 22).

Loeys–Dietz syndrome is caused by mutations in genes encoding compounds involved in the TGF-beta signaling pathway. Patients with this syndrome have tortuous arteries and arterial aneurysms with a high risk of arterial dissection or rupture. The risk remains high even in arteries that have normal diameters (2, 23).

Autosomal dominant polycystic kidney disease (ADPKD) was associated with SCAD in a few case reports. Patients with ADPKD have mutations in the polycystic kidney disease-1 and 2 genes that encode the polycystin synthesis. Polycystin is important for the integrity of the vascular wall, and its absence leads to vascular wall rupture and hemorrhage (2, 13).

1.4. Fibromuscular dysplasia

Fibromuscular dysplasia is the most frequently associated with SCAD in the literature. However, the most frequent clinical presentation of this arteriopathy is renovascular hypertension. The association with SCAD was first reported in 2011 by Saw et al. This is a disease of medium-sized artery walls that is not caused by atherosclerosis or inflammation. The highest incidence is found in middle-aged women who do not have many traditional risk factors. FMD is characterized by changes in the arteries, such as stenosis and aneurysms, which make arteries susceptible to dissection. The renal, cervico-cephalic, and visceral arteries are commonly involved (2, 10).

Angiographically, FMD has two types: multifocal, which is predominant, and unifocal. Between 41% and 86% of SCAD patients experience changes in other vascular beds, with the majority of them exhibiting changes in two or more extra-coronary vascular beds (29%–70%). The possible clinical manifestations of cervico-cephalic FMD could be ischemic stroke or subarachnoid bleeding due to arterial dissection or intra-cerebral aneurysm (2). Canadian authors reported the presence of cerebral aneurysm in 7.1% of SCAD patients (24).

In the American registry for FMD, the frequency of SCAD was less than 3%. Furthermore, in one large study with more than 60,000 ACS patients, it has been shown that 0.16% of cases caused by SCAD were linked with FMD. Even SLE, a specific systemic inflammatory disease, had a higher association rate with SCAD (13, 25, 26).

PHACTR1/EDN1 is a genetic locus on chromosome 6q24 which carries the risk for coronary artery disease and AMI (27). This gene is also associated with migraine and cervicocerebral artery dissection (CeAD) (28). The putative variant of the *PHACTR1* locus was found near a putative regulatory genetic region for *EDN1*, the *endothelin (ET)-1* gene. This putative PHACRT1 variant relates to the risk of FMD. Interestingly the rs9349379-A allele is linked with a higher risk for FMD, CeAD, and migraine, whereas the less common allele, rs9349379-G, is linked with an increased risk for atherosclerosis. Firstly, the determined genetic risk locus for SCAD is rs9349379. The link between SCAD and FMD was determined even on the genetic level. Gupta et al. found that the rs9349379-A allele is found more frequently in patients with lower levels of circulating ET-1 than in healthy population. Endothelin-1 is a potent vasoconstrictor, and its vascular effects could have an important role in the pathophysiology of SACD. Whether the ET-1 expression decreased in SCAD and FMD is still to be determined (7, 29, 30, 31).

1.5. Inflammatory conditions

In the literature, SCAD was closely linked with the systemic inflammatory conditions, and the highest incidence was reported in one Canadian series (in 8.9% of cases). However, the mechanistic link between those two pathological conditions is still unknown. Since 1982, SCAD has been associated with inflammatory processes. This connection was initially observed when arterial biopsies revealed a focal infiltration of the tunica adventitia with inflammatory cells, predominantly eosinophils (5). Hypothetically, they could release lytic enzymes, causing dissection (30, 31).

Common systemic inflammatory disorders associated with SCAD include systemic lupus erythematosus (SLE), rheumatoid arthritis, celiac disease, Crohn's disease, and ulcerative colitis (19). A sub-analysis of the Framingham offspring study reported that women with SLE have a 50-fold increased risk of MI compared with age-matched control. Having said that, only several case reports documenting the occurrence of SCAD in SLE patients were published. SCAD can be the first manifestation of SLE, and therefore, screening for this disease is prudent in these patients (2, 19). In the literature, we found different inflammatory diseases in patients with SCAD such as sarcoidosis and infective hepatitis. Polyarteritis nodosa with pathological changes in small- and medium-sized arteries has also been associated with SCAD (2, 32–34). In these case reports or case series, coronary vasculitis or systemic inflammation may explain the increased risk for SCAD. In the larger cohort studies, a rather small percentage of patients had inflammatory conditions or short-term increases in inflammatory markers. This systemic inflammatory disease could only be a coincidental finding (1). The authors did not find a connection between SCAD and vasculitis in systemic arteries in the conducted studies. Coronary arteritis is a rare pathological condition, and it is characterized by the stenosis or occlusion of the proximal parts of arteries accompanied by skip lesions or aneurysms. This finding is not characteristic of SCAD (31).

Recently, a case report of SCAD in COVID-19-infected patient was published. It is known that COVID-19 is inducing a marked inflammatory and immune response which can damage endothelial and smooth muscle cells in blood vessels. Theoretically, the inflammatory response induced by the infection could promote the fragility of coronary vessels and lead to SCAD (35).

Patients with autoimmune disorders have an increased risk for SCAD (1). The frequency of autoimmune diseases in SCAD patients is comparable with the frequency in the general population (approximately 9%) (36). A recent study using population-based data from the Rochester Epidemiology Project showed that patients with autoimmune diseases did not have an increased risk for SCAD (31).

1.6. Migraine

In SCAD cohort studies, the reported prevalence rate of migraine ranged from 37% to 46%, contrasting with a lifetime migraine prevalence rate of 24% in women from the Women's Ischemia Syndrome Evaluation (WISE) cohort in the United States. Female SCAD patients have an estimated 37% higher age-adjusted 1-year migraine prevalence rate, as reported (37). Migraine is characterized by headache, typically unilateral in location, accompanied by nausea/vomiting and sensitivity to loud sounds and lights (38). Studies showed that endothelial dysfunction in migraines could be involved in developing stroke and in the pathogenesis of cervical artery dissection. It is postulated that a similar association could be present in SCAD. In a study conducted by the Mayo Clinic research group found that migraines were highly prevalent among the female population with SCAD, as previously reported. The same researchers found that migraineurs with SCAD were younger with more prevalent arterial abnormalities. They more frequently complained of chest pain and depression. In a large US national cohort study with 66,360 SCAD patients, only 0.8% of patients had migraine (13).

1.7. Thyroid disorders

Patients with SCAD had a higher prevalence of hypothyroidism when compared with individuals with atherosclerosis who develop ACS. Among SCAD patients with hypothyroidism, there was a higher incidence among women, and they exhibited frequent dissection in the distal segments of coronary arteries as well as dissections in the corkscrew arteries. Therefore, they were more often treated conservatively. Thyroid hormones have a significant role in the heart and blood vessels. Hypothyroidism is accompanied by conduction disturbances, different types of arrhythmias, rapid atherogenesis, and coronary artery disease. The results from studies conducted on a small number of patients indicate that hypothyroidism may somehow be involved in SCAD pathophysiology. In those patients, even iatrogenic coronary artery dissection is more frequent (39). Also, Spanish authors found a high percentage of autoimmune thyroid dysfunction in the population with SCAD (40).

1.8 Inheritance and genetics

In ≤5% of SCAD cases, we found hereditary arteriopathies and connective tissue disorders (18). However, Goel et al. (41) published a case series with five pairs of relatives with angiographically confirmed SCAD.

Several studies investigating the susceptibility genes for SCAD were published in 2018 and 2019. The genes associated with the risk for SCAD were the *F11R* (the gene responsible for F11 receptor which is a regulator of tight junction assembly), *TLN1* (the gene encoding Talin 1 which is responsible for linking the actin cytoskeleton to the extracellular matrix), *TSR1* (the gene which influences ribosome maturation factor and RNA formation), already mentioned *PHACTR1* (the gene important for cytoskeleton actine), and *EDN1* (encoding endothelin 1 which is a circulating vasoactive peptide) (17).

Recently, Adlam et al. performed a meta-analysis of genome-wide association studies (GWAS) with approximately 2,000

patients with SCAD. The authors reported 17 risk genes and therefore polygenic inheritance for this disease. The genetics for atherosclerosis and SCAD showed some overlaps but in opposite directions. The genetic association was again confirmed for SCAD and FMD, but also for migraine and SCAD. Among the so-called new genes for SCAD, those associated with arterial hypertension gained more attention. It seems that there is a genetic link between arterial hypertension and the risk for developing SCAD. Strict control of arterial blood pressure could be pivotal in decreasing the risk of SCAD recurrence (42–44).

Published genetic data do not explain the female dominance demonstrated in this condition. This could be due to autosomal genes that have sex-related regulators (genes with estrogen-responsive structures) (17). Genetic testing for SCAD is not a standard practice, but it may be considered in situations where connective tissue diseases are suspected, as mentioned previously (18).

1.9. Atherosclerotic risk factors

Patients with SCAD have less percentage of the traditional cardiovascular risk factors for ischemic heart disease. New publications indicate that those patients could have traditional factors as well. In majority of them, hypertension, smoking, and dyslipidemia have been reported. However, no causal relationship has been found thus far (10, 18). According to a recently published study, SCAD patients exhibit arterial hypertension in approximately 37% of cases, while 35% have hyperlipidemia, which is almost identical as those observed in the population without SCAD (17, 45). Reasonably, those traditional risk factors for coronary artery disease are more common findings in older SCAD patients (10). It was reported that in a population involving over 600 SCAD patients, diabetes mellitus was identified in 0.9%–4.6% of cases, while smoking habits were observed in 0.6%–10% of patients. Consistent with earlier findings, hypertension was prevalent in 27%–36% of patients. Notably, obesity was not present in this population (46).

Arterial hypertension is highly prevalent in the general population. Also, high arterial systolic pressure and pulsatory pressure could cause SCAD by increasing the shear stress on the vessels. Notably, some psychosocial factors that are present predominantly in females could indirectly act by increasing the risk for hypertension, smoking, or abdominal obesity and therefore the risk for SCAD (46, 47).

In younger women, fat deposits primarily accumulates in the subcutaneous tissue, while in menopausal women, fat is starting to accumulate in visceral depots which is characteristic for men. In this way, the metabolic risk is increasing. Hormone replacement therapy with estrogen seems to recover the endothelial function in postmenopausal women (48). Visceral fat is an endocrine organ that releases adipokines and influences many metabolic pathways. Perivascular adipose tissue has effects on the development of atherosclerosis through inflammatory mechanisms, and it is also believed to play a significant role in SCAD development (49).

1.10. Mechanical stressors and exercise

The so-called mechanical stressors such as intense Valsalva-like maneuvers and factors that provoke coronary spasm have been reported in SCAD. In a recently published prospective studies with SCAD patients, the males in 11.9% of cases experienced chest pain immediately after isometric or intense physical activity (10). This physical stressor could induce a rise in catecholamine levels and a further increase in coronary artery shear stress, resulting to SCAD (18). Interestingly, the authors found retrograde SCAD on the coronary angiograms in Takotsubo syndrome associated with this type of stress (9). Sympathomimetic drugs such as amphetamines and cocaine have probably the same pathophysiology mechanisms in developing SCAD (15). The use of anabolic steroids, which could lead to the weakness of the arterial medial wall, in combination with intense physical activity (lifting weights) was reported in one case report as the cause of SCAD in a male patient (50). These substances enhance blood coagulability by reducing the production of plasminogen activator and influencing platelet function as well (51).

1.11. Emotional stressors

Preceding emotional stress has been described in a significant percentage of SCAD cases, particularly in women (10). Emotional distress, 24 h before ACS, was significantly more frequent in the SCAD group, but not in patients with type 1 MI. A high percentage of SCAD patients, 41%–55% in some published papers, have reported experiencing some kind of uncommon psychological stress prior to the occurrence of the event (3, 10).

It was reported that 40.5% of participants from a large prospective cohort study had some level of emotional stress followed by ACS, and 24% of patients were involved in physical activity, of whom 12.5% were engaged in isometric exercise. A smaller number of patients reported minor activities prior to SCAD such as severe coughing or vomiting. More recent studies reported that females with concomitant FMD and psychological stressors were at risk for SCAD. On the other part, men without FMD and physical stressors were at high risk for developing SCAD (13).

The results from a large Canadian study showed that men with SCAD were younger than females and that they more frequently had some physical but not psychological stressor preceding the ACS caused by SCAD (10). As mentioned, women with SCAD had a higher self-reported prevalence of anxiety and depression. Psychiatric disorders are known risk factors for bad prognosis and are linked with adverse cardiovascular events. There is a theory that women are more prone to psychological stressors which can lead to a rise in coronary artery shear stress and SCAD (12).

2. Discussion: clustering of SCAD risk factors

There were attempts to generate a risk model for developing SCAD. Smaardijk et al. (5) found that in included female

patients with SCAD, conventional cardiovascular risk factors were less frequent (<10%), except for arterial hypertension (in 31% of patients). Half of the patients had high levels of self-reported psychological stress; they were complaining of fatigue and burnout syndrome. The frequency of psychological diseases, such as anxiety and depression, was relatively low (9% and 12%). The authors extrapolated three risk factor "clusters": the first cluster was with FMD and non-conventional disorders such as tinnitus or chronic pain; the second "cluster" included migraine; and the third cluster was without any of these conditions.

Upon reviewing the existing literature, two distinct at-risk phenotypes for SCAD were identified: firstly, young women with antecedent psychological stressors, and secondly, middle-aged men with conventional risk factors, in whom the physical stressors preceded the event (8).

Giacalone et al. (46) recently divided the non-traditional risk factors in female patients as follows: "gender-specific," such as pregnancy; "gender-predominant," e.g., migraine; and "gender-related," including those diseases and stressors that affect women more often, e.g., depression, psychosocial risk factors such as partner violence or low socioeconomic status. Depression is an important risk factor for cardiovascular morbidity and mortality; however, there are substantial inconsistencies and variability in reporting the prevalence of depression and anxiety in patients with SCAD and those with atherosclerotic MI (3, 52). Data from a large US national database, including more than 66,000 patients with SCAD, showed that anxiety and depression were less frequent in SCAD patients compared with patients with atherosclerotic MI (30). Recently, Muphy et al. (53) found that among SCAD patients, there was a higher prevalence of anxiety, depression, and other psychological disturbances compared with atherosclerotic MI. There is a need for further research in this area, utilizing standardized questionnaires completed early after hospital admission and incorporating subsequent psychiatric evaluations.

In **Table 1**, we summarized the most common predisposing conditions, traditional risk factors for coronary artery disease, and precipitating factors that are associated with or preceding chest pain in SCAD patients.

SCAD incidence increased 10-fold in the last two decades. This could be attributed to a significant improvement in the diagnostic capabilities and increased awareness of this disease among healthcare providers. However, this disease is poorly studied and understood. In 2018, the American Heart Association (AHA) and the European Society of Cardiology (ESC) released expert consensus statements regarding SCAD. Subsequently, in 2019, Canadian authors published findings from a large multicenter, prospective registry focused on SCAD patients (54). These initiatives contribute significantly to and improve the awareness among healthcare providers regarding the diagnosis and management of SCAD patients.

Specifically, it all started with improved diagnostic techniques and defining the myocardial infarction with non-obstructive coronary arteries (MINOCA). It accounts for approximately 15% of all acute myocardial infarctions (AMI) and more frequently affects females. The pathogenesis of MINOCA is heterogeneous and may include atherosclerotic plaque rupture, plaque erosion with thrombosis, vasospasm, embolization, SCAD, or a combination of mechanisms. Non-vascular causes include acute myocarditis, Takotsubo syndrome, and non-ischemic cardiomyopathies which can mimic the clinical presentation. In one study, 67% of patients with initial MINOCA were reclassified after the cardiac magnetic resonance (CMR) evaluation. Combining optical coherence tomography (OCT) with CMR was shown to identify the majority of the underlying mechanisms of MINOCA. Furthermore, CMR-

TABLE 1 The common predisposing conditions, traditional risk factors, and precipitating factors in SCAD patients.

Predisposing conditions	Available evidence
Fibromuscular dysplasia	Multiple cohort studies
Coronary tortuosity and ectasia	Single cohort study (tortuosity), case reports (ectasia)
Pregnancy (antepartum, postpartum, multiple pregnancies)	Multiple cohort studies
Connective tissue disorders Marfan's syndrome Loeys–Dietz syndrome Ehler Danlos syndrome type IV (vascular type) Polycystic kidney disease	Single case reports or small case series Multiple cohort studies and single genetic study confirm rare association between SCAD and heritable connective tissue disorders
Hormonal imbalance/therapy Oral contraception Estrogen replacement therapy Clomiphene β-HCG Testosterone Polycystic ovarian syndrome	Female sex predominance in multiple cohort studies Associations with exogenous hormones limited to case reports and reported prevalence of hormone therapy in cohort studies
Systemic diseases Systemic lupus erythematodes Inflammatory bowel disease Polyarteritis nodosa Sarcoidosis Churg–Strauss syndrome Granulomatosis with polyangiitis (Wegener) Rheumatoid arthritis Takayasu arteritis Hypothyroidism Celiac disease Cryoglobulinemia	Reported increased prevalence of inflammatory conditions in cohort studies Single case reports or small case series
Traditional risk factors	
Arterial hypertension Hyperlipemia Depression (30) (ref)	Multiple cohort studies
Precipitating factors	
Intense exercise (isometric, aerobic)	Multiple cohort studies, single case reports, and small case series
Emotional stress	Multiple cohort studies
Coronary Spasm	Small case series
Recreational drugs Cocaine Amphetamines	Isolated cases in cohort studies and case reports
Valsalva type activities (sexual activity, vomiting, cough etc.)	Single case reports
Drugs: calcineurin inhibitors, 5-FU, fenfluramine, corticosteroids, methylphenidate, ergotamine, sumatriptan, dobutamine	Single case reports
Sleep deprivation	Single case report
Hypersensitivity reactions	Single case report

β-HCG, β-subunit of hCG gonadotropin; 5-FU, 5-fluorouracil.
Table was modified from Supplementary material online for: ESC-ACCA position statement on spontaneous coronary artery dissection: Eur Heart J 2018;39 (36):3353–3368.

confirmed diagnosis of MINOCA was associated with an increased risk of major adverse cardiovascular events at follow-up (55–58).

Computed tomography coronary angiography (CTCA) for the diagnosis of acute SCAD has the advantage of being non-invasive, without the increased risk of iatrogenic dissection. However, its role in acute setting is limited due to its reduced spatial resolution. Currently, it could play a role in the follow-up of SCAD patients (10, 59).

3. Conclusion

According to a recently conducted population-based analysis using the National Inpatient Sample (NIS), in-hospital mortality was higher in SCAD patients compared with patients with MI caused by atherosclerosis of coronary arteries (60). The logistic regression analysis identified atrial fibrillation, steroid use, ventricular arrhythmias, and cardiac arrest as significant predictors of intra-hospital mortality (8).

It is crucial to identify emotional and physical stressors that can trigger this not-so-rare disease, particularly in those with potential predisposing conditions such as FMD (21).

The classic angiographic characteristics of SCAD with defined intimal tear or spiraling dissection may not be evident, and intravascular ultrasound (IVUS) and optical coherence tomography should be used with extreme caution when SCAD is suspected (10, 59). The utilization of new imaging modalities and careful examination of patients with chest pain led to a better understanding of the SCAD pathophysiology and improved its diagnosis. However, there is a lack of randomized controlled studies for the treatment of SCAD, and further investigation is needed. Percutaneous coronary intervention is recommended only when patients have symptoms and signs of ongoing myocardial ischemia, or a large area of myocardium in jeopardy, and reduced antegrade flow (10).

SCAD has not been heavily linked to traditional risk factors, but it exhibits a strong association with specific comorbidities such as migraine and tinnitus, particularly in younger females who experience emotional triggers within 24 h preceding the ACS. This could be a profile that should be recognized by cardiologists leading to prompt diagnosis and appropriate treatment. These differences in profiling SCAD compared with atherosclerotic MI patients may decrease the occurrence of misdiagnosis and underdiagnosis of SCAD, hence improving its prognosis. Cardiac rehabilitation should be personalized for SCAD patients, and these patients should be educated regarding the known risk factors (3).

Author contributions

DS: Conceptualization, Supervision, Validation, Writing – original draft. SA: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. TK: Conceptualization, Writing – original draft, Writing – review & editing. VM: Conceptualization, Writing – original draft, Resources, Validation, Visualization. DK-K: Conceptualization, Writing – original draft, Writing – review & editing. MK: Conceptualization, Investigation, Writing – original draft, Resources, Supervision. JS: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. SM: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. BB: Conceptualization, Resources, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation*. (2018) 137(19): e523–57. doi: 10.1161/CIR.0000000000000564

2. Vandamme M, De Backer J, De Backer T, Drieghe B, Devos D, Gevaert S. The spectrum of spontaneous coronary artery dissection: illustrated review of the literature. *Acta Cardiol*. (2017) 72(6):599–609. doi: 10.1080/00015385.2017.1309095

3. Smaardijk VR, Mommersteeg PMC, Kop WJ, Pellegrini D, van Geuns RJ, Maas AHEM. Psychological and clinical characteristics of patients with spontaneous coronary artery dissection: a case–control study. *Int J Cardiol*. (2021) 323:1–6. doi: 10.1016/j.ijcard.2020.08.045

4. Matta A, Levai L, Elbaz M, Nader V, Parada FC, Carrié D, et al. Spontaneous coronary artery dissection: a review of epidemiology, pathophysiology and principles of management. *Curr Probl Cardiol*. (2023) 48(7):101682. doi: 10.1016/j.cpcardiol.2023.101682

5. Smaardijk VR, Mommersteeg PMC, Kop WJ, Adlam D, Maas AHEM. Psychological and clinical characteristics of female patients with spontaneous coronary artery dissection. *Neth Heart J*. (2020) 28(9):485–91. doi: 10.1007/s12471-020-01437-7

6. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best PJM. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol*. (2017) 70 (4):426–35. doi: 10.1016/j.jacc.2017.05.055

7. Adlam D, Olson TM, Combaret N, Kovacic JC, Iismaa SE, Al-Hussaini A, et al. Association of the PHACTR1/EDN1 genetic locus with spontaneous coronary artery dissection. *J Am Coll Cardiol*. (2019) 73(1):58–66. doi: 10.1016/j.jacc.2018.09.085

8. Ceriello L, Gallina S, Zimarino M. Spontaneous coronary artery dissection: not strictly a "benign female business". *Int J Cardiol*. (2020) 312:48–9. doi: 10.1016/j.ijcard.2020.04.026

9. Krittanawong C, Saw J, Olin JW. Updates in spontaneous coronary artery dissection. *Curr Cardiol Rep*. (2020) 22(10):123. doi: 10.1007/s11886-020-01378-y

10. Adlam D, Alfonso F, Maas A, Vrints C; Writing Committee. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. (2018) 39 (36):3353–68. doi: 10.1093/eurheartj/ehy080

11. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation*. (2012) 126:579–88. doi: 10.1161/CIRCULATIONAHA.112.105718

12. Sharma S, Kaadan MI, Duran JM, Ponzini F, Mishra S, Tsiaras SV, et al. Risk factors, imaging findings, and sex differences in spontaneous coronary artery dissection. *Am J Cardio*. (2019) 123(11):1783–7. doi: 10.1016/j.amjcard.2019.02.040

13. Khiatah B, Jazayeri S, Yamamoto N, Burt T, Frugoli A, Brooks DL. Cardiovascular disease in women: a review of spontaneous coronary artery dissection. *Medicine (Baltimore)*. (2022) 101(38):e30433. doi: 10.1097/MD.0000000000030433

14. Saw J, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv*. (2014) 7:645–55. doi: 10.1161/CIRCINTERVENTIONS.114.001760

15. Iyasere C, Potdar N. Spontaneous coronary artery dissection associated with infertility treatment. *Cureus*. (2022) 14(9):e29587. doi: 10.7759/cureus.29587

16. Abuzeyad FH, Ibnaouf ES, Farras MA. Clomiphene associated inferior STEMI in a young female due to right coronary artery dissection. *Case Rep Emerg Med*. (2017) 2017:4747831. doi: 10.1155/2017/4747831

17. Hayes SN, Tweet MS, Adlam D, Kim ESH, Gulati R, Price JE, et al. Spontaneous coronary artery dissection: JACC state-of-the-art review. *J Am Coll Cardiol*. (2020) 76 (8):961–84. doi: 10.1016/j.jacc.2020.05.084

18. Lewey J, El Hajj SC, Hayes SN. Spontaneous coronary artery dissection: new insights into this not-so-rare condition. *Annu Rev Med*. (2022) 73:339–54. doi: 10.1146/annurev-med-052819-023826

19. Janssen EBNJ, de Leeuw PW, Maas AHEM. Spontaneous coronary artery dissections and associated predisposing factors: a narrative review. *Neth Heart J*. (2019) 27(5):246–51. doi: 10.1007/s12471-019-1235-4

20. Combaret N, Gerbaud E, Dérimay F, Souteyrand G, Cassagnes L, Bouajila S, et al. National French registry of spontaneous coronary artery dissections: prevalence of fibromuscular dysplasia and genetic analyses. *Euro Intervention*. (2021) 17(6):508–15. doi: 10.4244/EIJ-D-20-01046

21. Becker AE, van Mantgem JP. The coronary arteries in Marfan's syndrome. A morphologic study. *Am J Cardiol*. (1975) 36:315–21. doi: 10.1016/0002-9149(75)90482-8

22. Reinhold SM, Lima B, Khalid A, Gonzalez-Stawinski GV, Stoler RC, Hall SA, et al. Heart transplantation in the Ehlers–Danlos syndrome. *Proc (Bayl Univ Med Cent)*. (2015) 28:492–3. doi: 10.1080/08998280.2015.11929319

23. Agrawal A, Baaj S, Schwartz J, Lopez JJ. Spontaneous coronary artery dissection in Loeys–Dietz syndrome: role of optical coherence tomography in diagnosis and management. *J Invasive Cardiol*. (2015) 27:E196–8.

24. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, et al. Canadian Spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J*. (2019) 40(15):1188–97. doi: 10.1093/eurheartj/ehz007

25. Kadian-Dodov D, Gornik HL, Gu X, Froehlich J, Bacharach JM, Chi YW, et al. Dissection and aneurysm in patients with fibromuscular dysplasia: findings from the U.S. registry for FMD. *J Am Coll Cardiol*. (2016) 68:176–85. doi: 10.1016/j.jacc.2016.04.044

26. Fahmy P, Prakash R, Starovoytov A, Boone R, Saw J. Pre-disposing and precipitating factors in men with spontaneous coronary artery dissection. *JACC Cardiovasc Interv*. (2016) 9:866–8. doi: 10.1016/j.jcin.2016.02.024

27. Kaadan MI, MacDonald C, Ponzini F, Duran J, Newell K, Pitler L, et al. Prospective cardiovascular genetics evaluation in spontaneous coronary artery dissection. *Circ Genom Precis Med*. (2018) 11:e001933. doi: 10.1161/CIRCGENETICS.117.001933

28. Poloskey SL, Kim ESh, Sanghani R, Al-Quthami AH, Arscott P, Moran R, et al. Low yield of genetic testing for known vascular connective tissue disorders in patients with fibromuscular dysplasia. *Vasc Med*. (2012) 17:371–8. doi: 10.1177/1358863X12459650

29. Myocardial Infarction Genetics Consortium; Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardissino D, Mannucci PM, et al. Genome wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nat Genet*. (2009) 41: 334–41. doi: 10.1038/ng.291

30. Krittanawong C, Kumar A, Johnson KW, Luo Y, Yue B, Wang Z, et al. Conditions and factors associated with spontaneous coronary artery dissection (from a national population-based cohort study). *Am J Cardiol*. (2019) 123 (2):249–53. doi: 10.1016/j.amjcard.2018.10.012

31. Kronzer VL, Tarabochia AD, Lobo Romero AS, Tan NY, O'Byrne TJ, Crowson CS, et al. Lack of association of spontaneous coronary artery dissection with autoimmune disease. *J Am Coll Cardiol*. (2020) 76(19):2226–34. doi: 10.1016/j.jacc.2020.09.533

32. Chu KH, Menapace FJ, Blankenship JC, Hausch R, Harrington T. Polyarteritis nodosa presenting as acute myocardial infarction with coronary dissection. *Cathet Cardiovasc Diagn*. (1998) 44:320–4. doi: 10.1002/(SICI)1097-0304(199807)44:3<320::AID-CCD16>3.0.CO;2-O

33. Karoglou S, Nair V, Fernandes JR. Sudden cardiac death due to coronary artery dissection as a complication of cardiac sarcoidosis. *Cardiovasc Pathol*. (2015) 24:244–6. doi: 10.1016/j.carpath.2015.01.001

34. Fernández-Gutiérrez B, Zamorano J, Batlle E, Alfonso F, Conde A, Sánchez-Harguindey L, et al. Coronary dissection associated with hepatitis C virus-related cryoglobulinaemia. *Rheumatology (Oxford)*. (1999) 38:1299–301. doi: 10.1093/rheumatology/38.12.1299

35. Shah N, Shah N, Mehta S, Murray E, Grodzinsky A. Spontaneous coronary artery dissection (SCAD) in an atypical patient without risk factors and prior asymptomatic COVID-19 infection. *Cureus*. (2023) 15(6):e40906. doi: 10.7759/cureus.40906

36. Funch D, Holick C, Velentgas P, Clifford R, Wahl PM, McMahill-Walraven C, et al. Algorithms for identification of Guillain–Barre syndrome among adolescents in claims databases. *Vaccine*. (2013) 31:2075–9. doi: 10.1016/j.vaccine.2013.02.009

37. Kok SN, Hayes SN, Cutrer FM, Raphael CE, Gulati R, Best PJM, et al. Prevalence and clinical factors of migraine in patients with spontaneous coronary artery dissection. *J Am Heart Assoc*. (2018) 7(24):e010140.

38. Pescador Ruschel MA, De Jesus O. *Migraine headache*. In: Pescador Ruschel MA, De Jesus O, editors. Statpearls [Internet]. Treasure Island (FL): StatPearls Publishing (2023). PMID: 32809622

39. Mantzoros CS, Evagelopoulou K, Moses AC. Outcome of percutaneous transluminal coronary angioplasty in patients with subclinical hypothyroidism. *Thyroid*. (1995) 5:383–7. doi: 10.1089/thy.1995.5.383

40. Camacho Freire SJ, Díaz Fernández JF, Gheorghe LL, Gómez Menchero AE, León Jiménez J, Roa Garrido J, et al. Spontaneous coronary artery dissection and hypothyroidism. *Rev Esp Cardiol (Engl Ed)*. (2019) 72(8):625–33. (English, Spanish). doi: 10.1016/j.rec.2018.06.031

41. Goel K, Tweet M, Olson TM, Maleszewski JJ, Gulati R, Hayes SN. Familial spontaneous coronary artery dissection: evidence for genetic susceptibility. *JAMA Intern Med*. (2015) 175(5):821–6. doi: 10.1001/jamainternmed.2014.8307

42. Georges A, Yang ML, Berrandou TE, Bakker MK, Dikilitas O, Kiando SR, et al. Genetic investigation of fibromuscular dysplasia identifies risk loci and shared genetics with common cardiovascular diseases. *Nat Commun*. (2021) 12(1):6031. Erratum in: Nat Commun. 2022 Apr 20;13(1):2251. doi: 10.1038/s41467-021-26174-2

43. Amrani-Midoun A, Adlam D, Bouatia-Naji N. Recent advances on the genetics of spontaneous coronary artery dissection. *Circ Genom Precis Med*. (2021) 14(6): e003393. doi: 10.1161/CIRCGEN.121.003393

44. Adlam D, Berrandou TE, Georges A, Nelson CP, Giannoulatou E, Henry J, et al. Genome-wide association meta-analysis of spontaneous coronary artery dissection identifies risk variants and genes related to artery integrity and tissue-mediated coagulation. *Nat Genet*. (2023) 55(6):964–72. doi: 10.1038/s41588-023-01410-1

45. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation* (2019) 139:e56–e528. doi: 10.1161/CIR.0000000000000659

46. Giacalone R, Ferretti M, Gurgoglione FL, Vezzani A, Pfleiderer B, Pela G, et al. Assessment of the role of nontraditional risk factors on spontaneous coronary artery dissections. *J. Clinical Cardiology and Cardiovascular Interventions*. (2022) 5(8). doi: 10.31579/2641-0419/289

47. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol*. (2017) 70:1148–58. doi: 10.1016/j.jacc.2017.06.053

48. Gambacciani M, Monteleone P, Vitale C, Silvestri A, Fini M, Genazzani AR, et al. Dydrogesterone does not reverse the effects of estradiol on endothelium dependant vasodilation in postmenopausal women: a randomised clinical trial. *Maturitas*. (2002) 43:117–23. doi: 10.1016/S0378-5122(02)00184-6

49. Meyer MR, Barton M. Role of perivascular adipose tissue for sex differences in coronary artery disease and spontaneous coronary artery dissection (SCAD). *Endocr Metab Sci*. (2021) 2:100068. doi: 10.1016/j.endmts.2020.100068

50. Heidari A, Sabzi F, Faraji R. Spontaneous coronary artery dissection in anabolic steroid misuse. *Ann Card Anaesth*. (2018) 21(1):103–4. doi: 10.4103/aca.ACA_161_17

51. Keir ML, Dehghani P. Corticosteroids and spontaneous coronary artery dissection: a new predisposing factor? *Can J Cardiol*. (2016) 32(3):395.e7–8. doi: 10.1016/j.cjca.2015.06.021

52. Pizzi C, Santarella L, Costa MG, Manfrini O, Flacco ME, Capasso L, et al. Pathophysiological mechanisms linking depression and atherosclerosis: an overview. *J Biol Regul Homeost Agents*. (2012) 26(4):775–82. doi: 10.1016/j.ijcard.2020.08.045

53. Murphy BM, Rogerson MC, Hesselson S, Iismaa SE, Hoover V, Le Grande M, et al. Prevalence of anxiety, depression, and distress in SCAD and non-SCAD AMI patients: a comparative study. *J Cardiopulm Rehabil Prev*. (2023) 43(5):338–45. doi: 10.1097/HCR.0000000000000782

54. Kim ESH, Tweet MS. Spontaneous coronary artery dissection: a call for consensus and research advancement. *J Am Coll Cardiol*. (2019) 74(10):1301–3. doi: 10.1016/j.jacc.2019.07.019

55. Reynolds HR, Maehara A, Kwong RY, Sedlak T, Saw J, Smilowitz NR, et al. Coronary optical coherence tomography and cardiac magnetic resonance imaging to determine underlying causes of myocardial infarction with nonobstructive coronary arteries in women. *Circulation*. (2021) 143(7):624–40. doi: 10.1161/CIRCULATIONAHA.120.052008

56. Bryniarski K, Gasior P, Legutko J, Makowicz D, Kedziora A, Szolc P, et al. OCT findings in MINOCA. *J Clin Med*. (2021) 10(13):2759. doi: 10.3390/jcm10132759

57. Gerbaud E, Arabucki F, Nivet H, Barbey C, Cetran L, Chassaing S, et al. OCT and CMR for the diagnosis of patients presenting with MINOCA and suspected epicardial causes. *JACC Cardiovasc Imaging*. (2020) 13(12):2619–31. doi: 10.1016/j.jcmg.2020.05.045

58. Mileva N, Paolisso P, Gallinoro E, Fabbricatore D, Munhoz D, Bergamaschi L, et al. Diagnostic and prognostic role of cardiac magnetic resonance in MINOCA: systematic review and meta-analysis. *JACC Cardiovasc Imaging*. (2023) 16(3):376–89. doi: 10.1016/j.jcmg.2022.12.029

59. Sultan A, Kreutz RP. Variations in clinical presentation, risk factors, treatment, and prognosis of spontaneous coronary artery dissection. *J Invasive Cardiol*. (2015) 27(8):363–9.

60. Mahmoud AN, Taduru SS, Mentias A, Mahtta D, Barakat AF, Saad M, et al. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: a population-based analysis. *JACC Cardiovasc Interv*. (2018) 11(1):80–90. doi: 10.1016/j.jcin.2017.08.016

frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 08 January 2024
DOI 10.3389/fcvm.2023.1280605

OPEN ACCESS

EDITED BY
Yoshiki Matsuo,
Kishiwada Tokushukai Hospital, Japan

REVIEWED BY
Matteo Armillotta,
University of Bologna, Italy
Sawan Jalnapurkar,
Gadsden Regional Medical Center,
United States
Christian Jörg Rustenbach,
University of Tübingen, Germany
Nino Cocco,
Campus Bio-Medico University Hospital, Italy

*CORRESPONDENCE
Gordana Krljanac
gkrljanac@gmail.com

RECEIVED 20 August 2023
ACCEPTED 19 December 2023
PUBLISHED 08 January 2024

CITATION
Krljanac G, Apostolović S, Polovina M, Maksimović R, Nedeljković Arsenović O, Đorđevic N, Stanković S, Savić L, Ušćumlić A, Stanković S and Ašanin M (2024) Differences in left ventricular myocardial function and infarct size in female patients with ST elevation myocardial infarction and spontaneous coronary artery dissection.
Front. Cardiovasc. Med. 10:1280605.
doi: 10.3389/fcvm.2023.1280605

Differences in left ventricular myocardial function and infarct size in female patients with ST elevation myocardial infarction and spontaneous coronary artery dissection

Gordana Krljanac[1,2]*, Svetlana Apostolović[3,4], Marija Polovina[1,2], Ružica Maksimović[2,5], Olga Nedeljković Arsenović[2,5], Nemanja Đorđevic[1], Stefan Stanković[1], Lidija Savić[1,2], Ana Ušćumlić[1,2], Sanja Stanković[6,7] and Milika Ašanin[1,2]

[1]Cardiology Clinic, University Clinical Center of Serbia, Belgrade, Serbia, [2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia, [3]Coronary Care Unit, Cardiology Clinic, University Clinical Center of Nis, Nis, Serbia, [4]Faculty of Medicine, University of Nis, Nis, Serbia, [5]Center for Radiology and Magnetic Resonance Imaging, University Clinical Center of Serbia, Belgrade, Serbia, [6]Center for Medical Biochemistry, University Clinical Center of Serbia, Belgrade, Serbia, [7]Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

Introduction: Differences in pathophysiology, clinical presentation, and natural course of ST-elevation myocardial infarction in female patients due to either spontaneous dissection (SCAD-STEMI) or atherothrombotic occlusion (type 1 STEMI) have been discussed. Current knowledge on differences in left ventricular myocardial function and infarct size is limited. The aim of this study was to assess baseline clinical characteristics, imaging findings, and therapeutic approach and to compare differences in echocardiographic findings at baseline and 3-month follow-up in patients with SCAD-STEMI and type 1 STEMI.

Methods: This was a prospective multicenter study of 32 female patients (18–55 years of age) presenting with either SCAD-STEMI due to left anterior descending coronary artery (LAD) dissection or type 1 STEMI due to atherothrombotic LAD occlusion.

Results: The two groups were similar in age, risk factors, comorbidities, and complications. SCAD-STEMI patients more often had Thrombolysis in Myocardial Infarction 3 flow, while type 1 STEMI patients were more often treated with percutaneous coronary intervention and dual antiplatelet therapy. Baseline mean left ventricular (LV) ejection fraction (LVEF) was similar in the two groups (48.0% vs. 48.6%, $p = 0.881$), but there was a significant difference at the 3-month follow-up, driven by an improvement in LVEF in SCAD-STEMI compared to type 1 STEMI patients (Δ LVEF $10.1 \pm 5.3\%$ vs. $1.8 \pm 5.1\%$, $p = 0.002$). LV global longitudinal strain was slightly improved in both groups at follow-up; however, the improvement was not significantly different between groups ($-4.6 \pm 2.9\%$ vs. $-2.0 \pm 2.8\%$, $p = 0.055$).

Conclusions: The results suggest that female patients with SCAD-STEMI are more likely to experience improvement in LV systolic function than type 1 STEMI patients.

KEYWORDS

spontaneous coronary artery dissection, myocardial infarction with ST-elevation, myocardial function, myocardial infarct size, echocardiography

1 Introduction

Distinct pathophysiological mechanisms underlying the development of type 1 ST-elevation myocardial infarction (STEMI) and myocardial infarction occurring due to spontaneous coronary artery dissection (SCAD), SCAD-STEMI, may be responsible for the differences in left ventricular (LV) function and myocardial infarct size in these two types of conditions (1, 2). Previous research findings suggested significant differences in the pathophysiology, clinical presentation, and natural course in female patients with ST-elevation myocardial infarction due to either spontaneous dissection (SCAD-STEMI) or atherothrombotic occlusion (type 1 STEMI) (3, 4).

Whether a more balanced process of infarct development in SCAD-STEMI could potentially result in smaller infarct sizes than the typical type 1 STEMI remains uncertain. It is important to note that the formation of myocardial infarction is a complex process. Contributing factors to infarct size include the type of infarct-related artery, severity and extent of coronary artery disease, location of the occlusion, the time it takes to restore blood flow by one of the revascularization procedures, and the overall health of the patient. In the case of SCAD-STEMI, various mechanisms may influence the infarct size, including the extent of the dissection, the occurrence of coronary artery healing, the presence of collateral blood flow, and the timing of coronary flow restoration (5). It is worth noting that most patients who present with SCAD typically have either small infarctions or no infarctions at all, and they also tend to have a preserved ejection fraction. However, those patients presenting as STEMI, Thrombolysis in Myocardial Infarction (TIMI) 0/1 flow at angiography, and/or multivessel SCAD are more likely to present with larger infarctions (5).

The aim of this research was to present baseline characteristics, risk factors, clinical findings, complications, laboratory analyses, and therapeutic approach and to compare differences in echocardiographic findings at baseline and 3-month follow-up in patients with SCAD-STEMI and type 1 STEMI.

2 Materials and methods

The study was conducted in 2023 at the University Clinical Centers in Belgrade and Nis, Serbia, as a prospective multicenter study. We included 32 consecutive adult female patients aged 18–55 years, presenting with either anterior SCAD-STEMI due to left anterior decedent coronary artery (LAD) dissection or type 1 STEMI due to atherothrombotic LAD occlusion. The patients were included prospectively between January 2023 and September 2023. The classification between SCAD-STEMI and type 1 STEMI was based on the findings of an emergency coronary angiography, which was performed at admission in all patients.

Patients who are either younger than 18 or older than 55 years; had a history of acute myocardial infarction (AMI) or coronary interventions, heart failure, uncontrolled hypertension, malignant diseases, obstructive pulmonary disease, hepatic or renal failure (eGFR ≤ 60 ml/min/1.73 m^2), acute or chronic infections, ketoacidosis; or were treated with corticosteroids or immunosuppressive agents were excluded from the study. All patients were referred for coronary angiography immediately after admission. All type 1 STEMI female patients were treated with percutaneous coronary interventions (PCIs) with successfully establishing TIMI 3 flow after intervention. Patients with SCAD-STEMI were treated with optimal medical therapy in accordance with recommendations in previous studies (6) except in the setting of SCAD type 4, active/ongoing ischemia, and hemodynamic instability. Upon admission, a complete medical history was obtained and a physical exam with anthropometric measurements was performed. Blood samples were taken for laboratory analysis during hospitalization. Comprehensive echocardiographic exams were performed by experienced cardiologists at baseline and after 3-month follow-up and compared between groups. Cardiac magnetic resonance (CMR) was performed in clinically and therapeutically disputed cases. A clinical 1.5-T scanner (Siemens Avanto) was used to perform CMR imaging. The imaging protocols were standardized and unified (University Clinical Center of Serbia, Center of CMR). The standard protocol for morphological and functional assessment was followed, which included late gadolinium enhancement (LGE), T1, and T2 mapping using the MOLLI sequence before and after contrast medium application. Myocardial T1 and T2 mapping was performed in long-axis directions and three short-axis slices (base level, midventricular, and apex level) using a validated variant of a modified Look-Locker Imaging sequence (University Clinical Center of Serbia, Center of CMR, MOLLI). Late gadolinium enhancement imaging was performed 10 min after the administration of 0.1 mmol/kg of body weight of gadobutrol (Gadovist; Bayer). The interpretation of LGE images followed standardized post-processing recommendations by two observers based on the presence and predominant pattern as ischemic or non-ischemic. The mean time for performance of CMR was 15 ± 7 days. There was no significant difference in the mean time from SCAD-STEMI/type 1 STEMI infarct onset to CMR performance.

All standard echocardiographic examinations were performed using Vivid E95 (General Electric). Data were acquired with a 3.5-MHz transducer in the parasternal (long- and short-axis views) and apical (four- and two-chamber and apical long-axis views) views, utilizing echocardiographic methods such as M-mode, 2D, color Doppler, pulse Doppler, continuous Doppler, tissue Doppler, and speckle-tracking imaging. All measurements and definitions were in accordance with the guidelines of the European and American Society of Echocardiography (7, 8).

Two-dimensional speckle-tracking echocardiography (2D-STE) is a non-invasive ultrasound imaging technique that allows for an objective and quantitative evaluation of global and regional myocardial deformation. It is also used to assess left ventricular (LV) systolic and diastolic myocardial function. The recordings were performed with a frame rate between 50 and 70 frames/s and analyzed offline using General Electric software (EchoPAC software version 203 GE Medical Systems). All

parameters of myocardial longitudinal strain were calculated offline in accordance with recommendation (9), and the global longitudinal strain (GLS) was analyzed on the 18-segment segmentation model.

Two to four weeks after the initial measurements, an echocardiographic exam, including strain analysis, was repeated in 10 randomly selected patients from both groups (SCAD-STEMI and type 1 STEMI) by the same observer (G.K.). The flow chart of the study is presented in Figure 1.

2.1 Statistical analyses

The continuous variables are presented as mean ± SD, while categorical data are presented as percentages. The differences between the groups at baseline were tested using a one-way analysis of variance (ANOVA), while the χ^2 test was used for categorical variables. We analyzed differences in 3-month follow-up echocardiographic parameters in 10 randomly selected patients from both groups (SCAD-STEMI and type 1 STEMI) by using the Student *t*-test. The statistical analyses were performed using SPSS software version 20.0 (SPSS Inc., USA) with a significance level set at $p < 0.05$.

3 Results

We analyzed two groups of female patients ≤55 years of age, presenting with either SCAD-STEMI due to LAD dissection or type 1 STEMI due to atherothrombotic LAD occlusion. As presented in Table 1, the two groups were similar with respect to age, risk factors, and comorbidities. However, patients with SCAD-STEMI had higher systolic and lower diastolic blood pressures and higher heart rates compared with type 1 STEMI patients.

There were no differences in the levels of high-sensitive troponin T (hs-troponin T), N-terminal pro-brain natriuretic peptide (NT-proBNP), and high-sensitive C reactive protein (hs-CRP) (Table 1). The frequency of symptomatic heart failure and arrhythmias occurring during the acute phase was similar between the groups. SCAD-STEMI patients more often had TIMI 3 flow at angiography as opposed to patients with type 1 STEMI, who more often had TIMI 0 flow. Furthermore, the use of reperfusion strategy with primary PCI was more frequent in patients with type 1 STEMI compared to SCAD-STEMI, as well as the use of dual antiplatelet therapy.

The results of the echocardiographic and CMR assessment of LV function at baseline of SCAD-STEMI and type 1 STEMI patients are presented in Table 2. Between-group comparisons at baseline showed no significant differences in clinical, echocardiographic, and CMR parameters, including infarct size at baseline, as assessed by the extent of LGE. The only observed difference at baseline was a higher LV mass index assessed by echocardiography in patients with type 1 STEMI (Table 2).

The results of comparisons in echocardiographic parameters between 10 randomly selected patients (from both groups) from baseline to the 3-month follow-up are presented in Table 3. There was a tendency toward a decrease in left ventricular end-diastolic volume (LVEDV)/left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume (LVESV)/left ventricular end-systolic volume index (LVESVI) in SCAD-STEMI patients, whereas there was a tendency toward an increase in LVEDV/LVEDVI and LVESV/LVESVI in type 1 STEMI patients (Table 3). However, the difference in LV volumes from baseline to 3-month follow-up was not statistically significant between the two groups (Table 3). There was a significant difference in left ventricular ejection fraction (LVEF) between the two groups, driven by the numerically greater improvement in LVEF in SCAD-STEMI patients than in type 1-STEMI patients (Table 3). Left ventricular global longitudinal strain (LVGLS) was not statistically different at follow-up between the two groups (Table 3).

Figure 2 illustrates the changes in myocardial function (LVEF and LVGLS) in two female patients, one with SCAD-STEMI and the other with type 1 STEMI, assessed from baseline to the 3-month follow-up.

In the Supplementary Material, we also illustrate CMR differences in the distribution of LGE at baseline in a type 1 STEMI patient and a SCAD-STEMI patient (Supplementary Figure S1) as well as in other CMR findings (Supplementary Figures S2, S3).

4 Discussion

In this prospective study, we compared female patients with SCAD-STEMI and type 1 STEMI with culprit LAD by analyzing their clinical features and imaging findings at baseline and the 3-month follow-up. Our results suggest that patients with SCAD-STEMI, despite having similar baseline clinical characteristics, estimates of infarct size (LGE), and LV function to type 1 STEMI patients, might have a more favorable trajectory of LV remodeling over the 3-month follow-up. Although the observed differences in LV volumes between the two patient groups were not significant at 3-month follow-up, patients with SCAD-STEMI experienced a net decrease in LV volumes, which was not observed in type 1 STEMI patients. There was a significant difference in LVEF at 3-month follow-up between the two groups due to a greater net improvement in LVEF in SCAD-STEMI patients compared with the type 1 STEMI group. LVGLS was not significantly different, albeit both groups showed signs of some improvement in myocardial strain at 3-month follow-up.

Previous studies suggested that clinical, electrocardiographic, and echocardiographic findings may be similar in SCAD-STEMI and type 1 STEMI patients, which may carry a risk of an inaccurate diagnosis or inadequate treatment if the two conditions are not differentiated (10, 11). It is also important to consider that clinical presentation of both SCAD-STEMI and type 1 STEMI can vary widely among individuals, and infarct size might not always follow a clear pattern based solely on the pathophysiology of myocardial infarction (5). Of note, SCAD is a

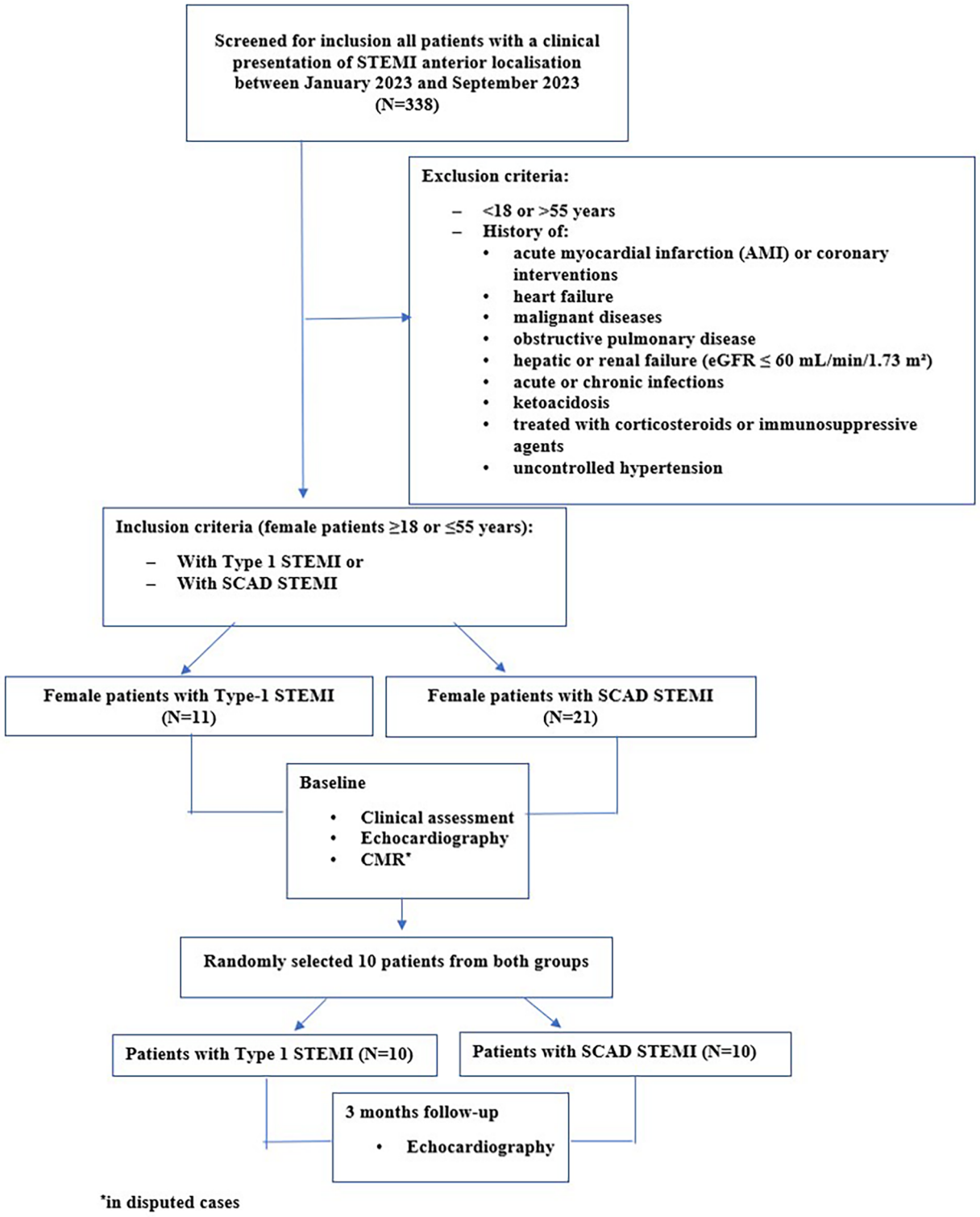


FIGURE 1
Flowchart of the study.

condition that occurs more frequently in women and is the prevailing cause of myocardial infarction in young and middle-aged females without cardiovascular risk factors (1). It is often precipitated by stressful situations, strenuous exercise, hormonal changes, pregnancy, vasospasm, connective tissue disorders, fibromuscular dysplasia, and the use of certain medications or drug abuse (cocaine) (1, 3). In addition, depression has been described as a risk factor not only associated with a higher risk of SCAD but also with the development and progression of atherosclerosis, potentially leading to type 1 myocardial infarction (12).

10.3389/fcvm.2023.1280605

TABLE 1 Baseline clinical and laboratory characteristics, risk factors, and therapeutic approaches in SCAD-STEMI and type 1 STEMI groups of patients.

	SCAD-STEMI ($n = 11$)	Type 1 STEMI ($n = 21$)	p
Age, years (mean ± SD)	45.1 ± 7.3	46.2 ± 6.7	0.671
BMI, kg/m^2 (mean ± SD)	24.8 ± 4.2	26.1 ± 4.1	0.516
Hypertension (%)	47.4	66.7	0.339
Hyperlipidemia (%)	33.3	22.2	0.535
Diabetes (%)	0	0	1.000
Renal insufficiency (%)	0	0	1.000
Family history of coronary diseases (%)	0	22.2	0.125
Smoking (%)	33.3	66.7	0.100
Stressful situation (%)	27.3	23.9	0.830
Pregnancies/postpartum (%)	18.2	4.8	0.216
Systolic BP, mmHg (mean ± SD)	147.5 ± 32.2	122.2 ± 23.5	**0.049**
Diastolic BP, mmHg (mean ± SD)	67.3 ± 19.4	73.3 ± 9.1	**0.022**
Heart rate, bpm (mean ± SD)	82.5 ± 14.1	71.5 ± 8.1	**0.027**
SCAD type (%)	/	/	
1	18.2		
2	36.3		
3	27.3		
4	18.2		
TIMI (0/1/2/3) (%)			**0.012**
0	27.3	81.0	
1	18.1	9.5	
2	27.3	9.5	
3	27.3	0	
Localization of occlusion, n (%)			0.420
LAD	11 (100)	18 (85.7)	
LAD + Cx	0	2 (9.5)	
LAD + D1	0	1 (4.8)	
Time from symptom onset to PCI center admission, h (mean ± SD)	2.97 ± 2.06	2.60 ± 2.70	0.499
Heart failure (Killip class ≥ 2) (%)	22.2	10.5	0.409
Arrhythmia (%)			
Ventricular tachycardia	22.2	47.6	0.193
Ventricular fibrillation	12.5	19.0	0.677
Atrial fibrillation	0	5.3	0.600
High-sensitivity troponin T (ng/L)	1,407.7 ± 410.9	1,833.7 ± 600.0	0.716
Creatine kinase (U/L)	867.7 ± 206.1	1,894.4 ± 468.0	0.208
NT-pro BNP (pg/ml)	174.6 ± 123.5	1,401.4 ± 700.7	0.187
Total cholesterol (mmol/L)	4.6 ± 0.7	4.9 ± 1.6	0.730
High-density lipids (mmol/L)	1.7 ± 0.4	1.2 ± 0.4	**0.029**
Low-density lipids (mmol/L)	2.4 ± 0.5	3.2 ± 1.1	0.163
Triglyceride (mmol/L)	1.2 ± 0.4	1.1 ± 0.5	0.735
hs-CRP (ng/L)	55.9 ± 33.1	27.5 ± 14.8	0.374
Aspirin (%)	81.8	90.5	0.482
P2Y12 inhibitors (%)			
Clopidogrel	72.7	33.3	**0.006**
Ticagrelor	0	57.2	
Anticoagulant therapy (%)	72.7	90.5	0.135
ACE inhibitors (%)	45.5	81.0	**0.040**
BB (%)	54.5	85.7	0.053
Statins (%)	45.5	90.5	**0.005**
PCI (stent/POBA) (%)	36.4	100	**0.001**

BB, beta-blockers; BMI, body mass index; BP, blood pressure; Cx, circumflex coronary artery; D1, first diagonal branch coronary artery; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; POBA, balloon angioplasty without a stent.
Bold values denote significant differences ($p < 0.05$).

TABLE 2 Differences in echocardiographic and CMR parameters between SCAD-STEMI and type 1 STEMI patients at baseline.

Baseline echocardiography	SCAD-STEMI ($n = 11$)	STEMI type 1 ($n = 21$)	p
LVEDD (cm)	4.9 ± 0.4	5.0 ± 0.6	0.968
LVESD (cm)	3.2 ± 0.4	3.2 ± 0.8	0.879
LVIVS (cm)	0.98 ± 0.17	0.98 ± 0.19	0.155
LVPW (cm)	0.87 ± 0.15	0.95 ± 0.14	0.137
LV mass index (g/m^2)	72.2 ± 14.0	97.6 ± 21.4	**0.019**
WMI	1.48 ± 0.43	1.51 ± 0.43	0.859
Peak E wave velocity (m/s)	0.66 ± 0.16	0.58 ± 0.17	0.255
Peak A wave velocity (m/s)	0.62 ± 0.15	0.62 ± 0.12	0.993
E/A ratio	1.10 ± 0.44	0.91 ± 0.42	0.277
Peak e′ medial velocity (cm/s)	6.5 ± 1.3	7.7 ± 3.0	0.433
Peak e′ lateral velocity (cm/s)	8.5 ± 1.9	8.5 ± 3.1	0.989
E/e′ average ratio	7.7 ± 2.6	7.8 ± 1.6	0.958
LAV (ml)	40.5 ± 7.6	32.5 ± 12.8	0.242
LAVI (ml/m^2)	23.2 ± 5.1	18.2 ± 6.7	0.168
LVEDV (ml)	122.3 ± 18.3	101.5 ± 39.8	0.112
LVEDVI (ml/m^2)	60.0 ± 16.6	54.3 ± 31.4	0.073
LVESV (ml)	69.5 ± 8.3	56.5 ± 19.8	0.579
LVESVI (ml/m^2)	33.7 ± 9.2	30.2 ± 16.1	0.511
LVEF (%)	48.0 ± 7.1	48.6 ± 11.4	0.881
LVGLS (%)	−14.0 ± 2.77	−13.3 ± 4.5	0.630
Baseline CMR	**SCAD-STEMI ($n = 10$)**	**STEMI type 1 ($n = 10$)**	**p**
LVEDV (ml)	144.2 ± 36.5	151.8 ± 28.2	0.789
LVEDVI (ml/m^2)	83.3 ± 17.8	82.4 ± 10.8	0.948
LVESV (ml)	72.1 ± 33.8	75.7 ± 26.1	0.892
LVESVI (ml/m^2)	41.3 ± 18.1	42.0 ± 13.7	0.958
LVEF (%)	50.8 ± 11.1	43.3 ± 13.3	0.495
LGE (%)	10.0 ± 8.8	14.3 ± 6.6	0.536

LAV, left atrial velocity; LAVI, left atrial velocity index; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVIVS, left ventricular interventricular septum dimension; LVPW, left ventricle posterior wall dimension; WMI, wall motion index.
Bold values denote significant differences ($p < 0.05$).

TABLE 3 Improvements of echocardiographic parameters after 3-month follow-up in SCAD-STEMI patients and type 1 STEMI patients.

Δ (3-month FU—baseline)	SCAD-STEMI ($n = 10$)	Type 1 STEMI ($n = 10$)	p
Δ LVEDV, ($LVEDV_2 - LVEDV_1$) (ml)	−11.6 ± 21.9 (107.2 ± 32.6)—(118.9 ± 18.9)	8.4 ± 28.3 (125.2 ± 40.7)—(117.2 ± 52.9)	0.122
Δ LVEDVI, ($LVEDVI_2 - LVEDVI_1$) (ml/m^2)	−10.9 ± 13.7 (57.3 ± 17.1)—(68.1 ± 8.3)	3.9 ± 15.3 (67.7 ± 18.1)—(63.8 ± 26.1)	0.055
Δ LVESV, ($LVESV_2 - LVESV_1$) (ml)	−11.8 ± 16.3 (49.6 ± 17.3)—(61.5 ± 19.5)	1.1 ± 22.6 (64.0 ± 33.9)—(62.9 ± 44.4)	0.200
Δ LVESVI, ($LVESVI_2 - LVESVI_1$) (ml/m^2)	−7.8 ± 9.7 (26.8 ± 9.6) —(34.6 ± 10.7)	0.3 ± 11.8 (34.2 ± 16.5)—(33.9 ± 22.5)	0.150
Δ LVEF, ($LVEF_2 - LVEF_1$) (%)	10.1 ± 5.3 (57.7 ± 7.2) —(47.6 ± 7.3)	1.8 ± 5.1 (52.6 ± 11.3) —(50.8 ± 11.8)	**0.002**
Δ LVGLS, ($LVGLS_2 - LVGLS_1$) (%)	−4.6 ± 2.9 (−18.1 ± 3.9)—(−13.4 ± 2.1)	−2.0 ± 2.8 (−16.2 ± 6.5)—(−14.2 ± 4.9)	0.055

FU, follow-up; $LVEDV_1$, left ventricular end-diastolic volume at baseline; $LVEDV_2$, left ventricular end-diastolic volume after 3-month FU; $LVEDVI_1$, left ventricular end-diastolic volume index at baseline; $LVEDVI_2$, left ventricular end-diastolic volume index after 3-month FU; $LVEF_1$, left ventricular ejection fraction at baseline; $LVEF_2$, left ventricular ejection fraction after 3-month FU; $LVESV_1$, left ventricular end-systolic volume at baseline; $LVESV_2$, left ventricular end-systolic volume after 3-month FU; $LVESVI_1$, left ventricular end-systolic volume index at baseline; $LVESVI_2$, left ventricular end-systolic volume index after 3-month FU; $LVGLS_1$, left ventricular global longitudinal strain at baseline; $LVGLS_2$, left ventricular global longitudinal strain after 3-month FU.
Bold values denote significant differences ($p < 0.05$).

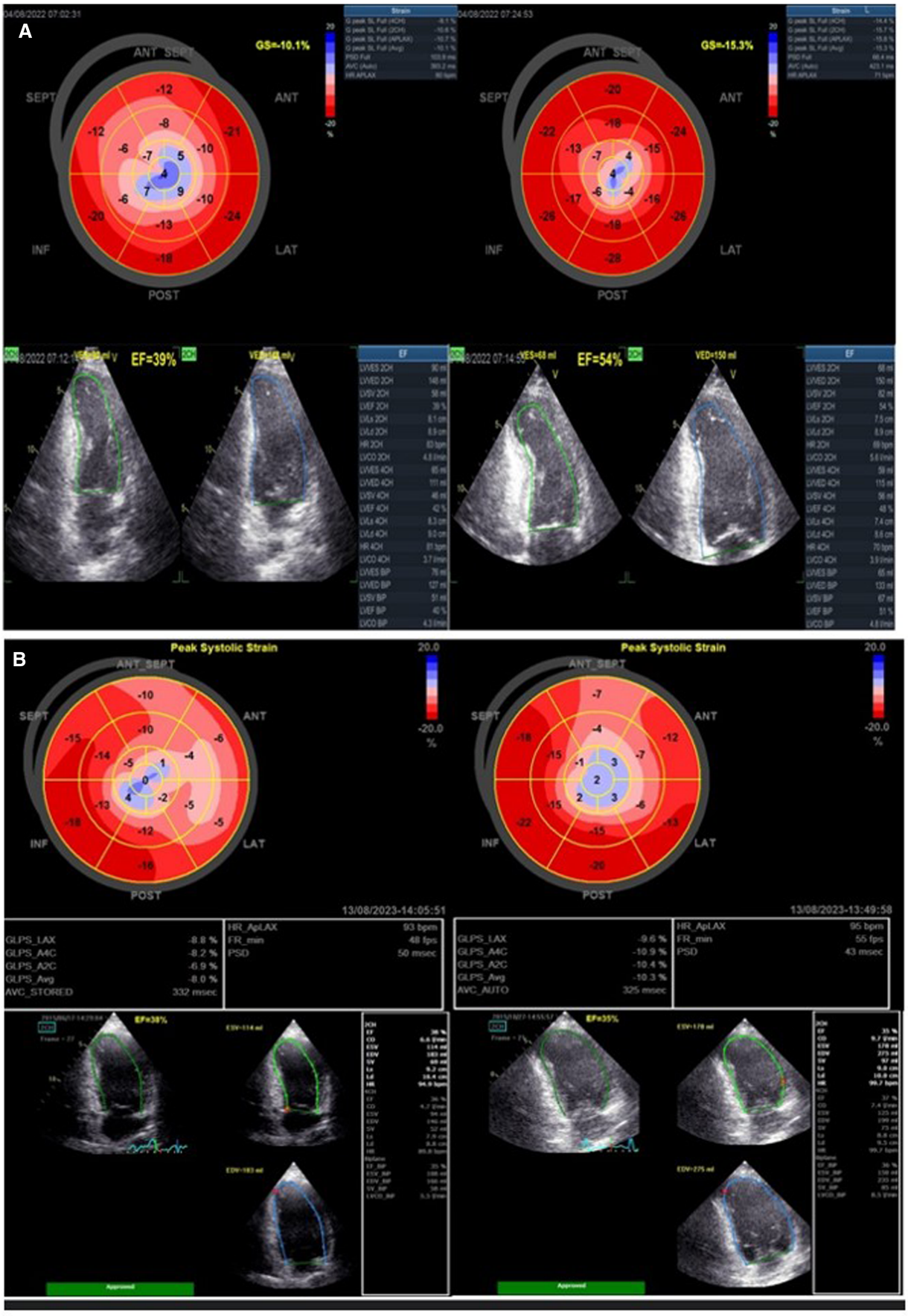

A
GS=-10.1%
GS=-15.3%
ANT SEPT
SEPT
ANT
INF
LAT
POST
EF=39%
EF=54%
B
Peak Systolic Strain
13/08/2023-14:05:51
13/08/2023-13:49:58

FIGURE 2
(A) A 42-year-old woman presented with STEMI anterior localization SCAD on left anterior artery type 4 and TIMI flow 0, treated with percutaneous transluminal coronary angioplasty (PTCA) without implantation of stents. Baseline LVEF was 39% and LVGLS was −10.1%. After 3-month follow-up, the LVEF was 54% and LVGLS was −15.3%. (B) A 29-year-old woman presented with type 1 STEMI anterior localization due to occluded LAD treated with primary PCI and implantation of two stents. Baseline LVEF was 35% and LVGLS was −8.0%. After 3-month follow-up, the LVEF was 36% and LVGLS was −10.3%.

Although our study had a small sample size for the two groups of females ≤55 years old, it is still informative to note that the two groups were well-balanced in baseline characteristics, risk factors, laboratory analyses, and immediate clinical course. However, there were significant differences in TIMI flow on angiography (i.e., type 1 STEMI patients more often had TIMI 0 flow) and reperfusion strategy treatment with primary PCI, and the use of dual antiplatelet therapy was more frequent in patients with type 1 STEMI.

4.1 Pathophysiological characteristics in SCAD-STEMI

The pathophysiological mechanisms underlying SCAD-STEMI and type 1 STEMI conditions differ, which may result in differences in infarct size and post-infarction LV remodeling. Although an intimal tear represents the most frequent cause of SCAD, causing a formation of a false lumen in the medial layer, coronary intramural hematoma without an intimal tear was also documented with the use of intravascular ultrasonography (10,11, 13) and later confirmed by high-resolution optical coherence tomography (14). The primary cause of an AMI in SCAD is the obstruction of a coronary artery due to either the compression of the artery's true lumen by a dissection flap or the expansion of a hematoma within the arterial wall. However, subsequent SCAD healing and a conditioning effect on the myocardium by coronary artery collateralization induced by prior fixed stenosis (similar to type 1 STEMI) may have an impact on the infarct size in SCAD-STEMI (5). These explanations point to a dynamic interplay of mechanisms affecting the infarct size in SCAD-STEMI (5).

4.2 SCAD type by angiography and formation of myocardial infarction

The SCAD type by angiography may also have an impact on the formation of myocardial infarct size. In our study, 18.2% of patients had SCAD type 1; 36.3% of patients had SCAD type 2; 27.3% SCAD type 3; and 18.2% of patients who went directly to PCI and revascularization had SCAD type 4. In SCAD type 1, the longitudinal filling defect can be detected due to the formation of an intimal flap (15). SCAD type 2 (the most common presentation) is characterized by a diffuse, long, smooth tubular stenosis caused by intramural hematoma without an apparent dissection (15). Type 1 and 2 SCAD patients may result in smaller myocardial infarction size, which may explain the more favorable resolution of myocardial infarct size and improvement in parameters of LV function in SCAD-STEMI patients in our study. Most experts believe that intramural hematoma is the initial mechanism in most SCAD and that there would be some time interval between intramural hematoma generation (type 2 lesion) and the development of a type 1 lesion (16). This concept may explain findings that type 1 lesions were more frequently found in "late presenters" in whom SCAD lesions had more time to produce myocardial ischemia and/or necrosis (16). In addition, myocardial infarction size further depends on the characteristics of coronary vessel involvement, with larger infarctions caused by the proximal, multi-segment and/or multivessel SCAD (5). SCAD type 3 can occur due to focal or multiple tubular lesions, usually <20 mm long, caused by intramural hematoma that can mimic atherosclerosis and require intravascular imaging for diagnosis (15). The increase in the severity of coronary artery stenosis and the presence of fenestrated and non-fenestrated types of stenosis can also influence the infarct size (14). SCAD type 4 has been described as a complete vessel occlusion (17). Patients with SCAD type 4 exhibit similarities with type 1 STEMI patients in myocardial infarct size, and it seems that these patients have larger myocardial infarctions than SCAD type 1 and 2 patients. In patients with SCAD associated with poor TIMI flow, who are at an increased risk of developing a larger infarct size, the therapeutic strategy may favor interventional management over conservative treatment (17).

4.3 Imaging methods for quantifying myocardial infarct size and myocardial perfusion in SCAD-STEMI due to LAD dissection and type 1 STEMI due to LAD occlusion

Myocardial infarct size can be quantified with a high degree of precision using CMR imaging by a semi-automatic method with LGE (18). CMR-quantified infarct size can be categorized as large (LGE mass accounting for >10% of the total LV mass) or small (LGE mass accounts for ≤10% of the total LV mass) (5). In the case of SCAD-STEMI patients, earlier research demonstrated a trend toward smaller myocardial infarct size and reduced levels of LGE with both endocardial and transmural involvement, in comparison to the type 1 STEMI patients where the characteristic pattern of LGE involved subendocardial distribution (19). However, in our study, baseline CMR-LGE values were not significantly different between the two groups.

Besides CMR, stress-test perfusion CMR, single-photon emission computed tomography or positron emission tomography myocardial perfusion imaging, and intravascular Doppler ultrasound coronary flow reserve can be used to further assess myocardial infarct size and blood flow and identify areas of reduced myocardial perfusion caused by SCAD (20–23). The imaging modalities are particularly valuable in assessing coronary microvascular dysfunction, however, with caveats imposed by limited availability and optimal timing of the assessment following a SCAD event. Stress perfusion tests are contraindicated in the acute phase of the disease, but they can be useful later in the follow-up of SCAD patients. Reassessment of cardiac function at 3 months is appropriate for patients with reduced LV function at the time of an AMI (24). Further limitations include breast or soft tissue attenuation and reduced accuracy in patients with smaller-sized hearts, which are more commonly seen in women than men (25).

4.4 Imaging methods for the assessment of myocardial function in SCAD-STEMI due to LAD dissection and type 1 STEMI due to atherothrombotic LAD occlusion

CMR is regarded as a standard reference method for the assessment LV myocardial function after an AMI (26). Cine-imaging CMR has been previously used to determine LV volumes and global and regional function at baseline and follow-up (5). Echocardiography is a more available but less accurate method for the assessment of LV function compared with CMR. The study by Franco et al. (27) suggested that approximately 26% of SCAD patients had a slightly reduced LVEF below 50% and approximately 5.1% had an LVEF below 40%. In the Spanish Registry of SCAD patients (SR-SCAD), patients with SCAD and reduced LVEF <50% presented more often with an anterior STEMI and multi-segment involvement coronary artery disease (16). These findings are in line with our observations. In the present study, the mean values of LVEF at the baseline were below 50% in both groups (48.0% vs. 48.6%, SCAD-STEMI vs. STEMI type 1). At 3-month follow-up, we found that the mean values had increased to >50% in both groups (57.7 vs. 52.6%, SCAD-STEMI vs. type 1 STEMI). We used LVGLS in this study because it can provide more precise prognostic information in SCAD survivors, particularly those with an LVEF > 50%, compared with other imaging options (28, 29). Although there were no statistically significant differences between the two groups both at baseline and 3-month follow-up in LVGLS, some improvement was observed in LVGLS in both groups over time. It remains to be determined whether strain echocardiography can add to the monitoring of patients with SCAD, considering the limited availability of those other diagnostic methods, such as CMR, in everyday practice.

A previous position paper recommended that SCAD patients who are experiencing recurrent chest pain should be carefully assessed via serial electrocardiography (ECG), high-sensitivity troponin measurement, and coronary angiography imaging in accordance with the physician's assessment (15). Therefore, the significance of the assessment of LV systolic function and myocardial infarct size is high and mandatory to guide further pharmacological and non-pharmacological management. First, early CMR imaging in SCAD-STEMI patients may provide identification of high-risk markers for future adverse cardiac events. Second, there is a need for continued and extended monitoring of SCAD-STEMI patients beyond 3 months to enable a more comprehensive assessment of their cardiac function and identification of long-term complications, including the development of heart failure (HF).

5 Study limitations

Several limitations of the present study need to be acknowledged. The most important limitation is a small sample size; however, the study was prospective and multicenter, which mitigates the limitation imposed son the generalizability of our findings. Furthermore, we only analyzed female patients ≤55 years old, which limits generalization to older women or men. Another limitation is that we did not perform CMR in all patients at baseline, which imposes a caveat in the interpretation of CMR estimated infarct sizes (extent of LGE) between the two groups. The study is also limited by short follow-up time. However, using one of the more sophisticated echocardiographic imaging methods, we managed to find a difference in myocardial function between the two observed groups. Considering the limitations of our study, its findings should be regarded as hypothesis generating, pending further confirmation from larger analyses.

6 Conclusions

The results of the present study suggest that young and middle-aged female patients with SCAD-STEMI exhibit a tendency for an improvement in LV systolic function during the prospective follow-up, which was more substantial in comparison to patients with type 1 STEMI. These differences may be related to a greater prevalence of TIMI 3 flow at angiography in SCAD-STEMI patients, subsequent healing of the dissected artery, and an overall smaller ischemic burden in SCAD-STEMI compared with type 1 STEMI patients. However, this may not be the case with the more complex types of SCAD, involving total vessel occlusion and multisegmented or multivessel engagement. Multimodality imaging, such as standard and strain echocardiography and CMR, may play a valuable role in the initial evaluation and follow-up of patients with SCAD-STEMI and in the assessment of the trajectory of LV remodeling following SCAD-STEMI, which may have important therapeutic and prognostic implications.

Author contributions

GK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – original draft. SA:

Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. MP: Conceptualization, Formal Analysis, Investigation, Software, Supervision, Writing – original draft. RM: Supervision, Visualization, Writing – review & editing. ON: Data curation, Methodology, Validation, Visualization, Writing – original draft. NĐ: Conceptualization, Formal Analysis, Writing – original draft. SS: Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. LS: Conceptualization, Data curation, Formal Analysis, Resources, Software, Writing – original draft. AU: Conceptualization, Data curation, Formal Analysis, Investigation, Writing – original draft. SS: Data curation, Formal Analysis, Writing – original draft. MA: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Validation, Writing – review & editing.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1280605/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Two middle age females with STEMI presentation on CMR. Panel A and C presented a short axis and 4-chamber view of the left ventricle (LV) of female 48 years old with type-1 STEMI and occluded LAD treated with primary percutaneous coronary intervention (PCI) and implantation 3 stents in LAD. Panel B and D presented a short axis and 4-chamber views of LV of a female 42 years old presented with SCAD-STEMI due to type 4 LAD dissection treated with percutaneous balloon dilatation without stent implantation.

SUPPLEMENTARY FIGURE S2
Additional CMR findings of the female patients in Figure 3.

SUPPLEMENTARY FIGURE S3
Female with SCAD type 2 and TIMI 3 with preserved LVEF, without abnormal contractility, and without CMR LGE verification.

References

1. Kim ESH. Spontaneous coronary-artery dissection. *N Engl J Med*. (2020) 24:2358–70. doi: 10.1056/NEJMra2001524

2. Basso C, Morgagni GL, Thiene G. Spontaneous coronary artery dissection: a neglected cause of acute myocardial ischaemia and sudden death. *Heart*. (1996) 75:451–4. doi: 10.1136/hrt.75.5.451

3. Adlam D, Alfonso F, Maas A, Vrints C. European Society of Cardiology, Acute Cardiovascular Care Association, SCAD Study Group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. (2018) 39:3353–68. doi: 10.1093/eurheartj/ehy080

4. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation*. (2018) 137:e523–57. doi: 10.1161/CIR.0000000000000564

5. Al-Hussaini A, Abdelaty A, Gulsin GS, Arnold JR, Garcia-Guimaraes M, Premawardhana D, et al. Chronic infarct size after spontaneous coronary artery dissection: implications for pathophysiology and clinical management. *Eur Heart J*. (2020) 41:2197–205. doi: 10.1093/eurheartj/ehz895

6. Krittanawong C, Gulati R, Eitzman D, Jneid H. Revascularization in patients with spontaneous coronary artery dissection: where are we now? *J Am Heart Assoc*. (2021) 10:e018551. doi: 10.1161/JAHA.120.018551

7. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. (2015) 16:233–71. doi: 10.1016/j.echo.2014.10.003

8. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. (2017) 18:1301–10. doi: .org/10.1093/ehjci/jex244

9. Voigt J-U, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/industry task force to standardize deformation imaging. *Eur Heart J Cardiovasc Imaging*. (2015) 16:1–11. doi: .org/10.1093/ehjci/jeu184

10. Kearney P, Erbel R, Ge J, Zamorano J, Koch L, Görge G, et al. Assessment of spontaneous coronary artery dissection by intravascular ultrasound in a patient with unstable angina. *Cathet Cardiovasc Diagn*. (1994) 32:58–61. doi: 10.1002/ccd.1810320114

11. Maehara A, Mintz GS, Castagna MT, Pichard AD, Satler LF, Waksman R, et al. Intravascular ultrasound assessment of spontaneous coronary artery dissection. *Am J Cardiol*. (2002) 89:466–8. doi: 10.1016/s0002-9149(01)02272-x

12. Pizzi C, Santarella L, Costa MG, Manfrini O, Flacco ME, Capasso L, et al. Pathophysiological mechanisms linking depression and atherosclerosis: an overview. *J Biol Regul Homeost Agents*. (2012) 26(4):775–82.

13. Saw J, Mancini GBJ, Humphries K, Fung A, Boone R, Starovoytov A, et al. Angiographic appearance of spontaneous coronary artery dissection with intramural hematoma proven on intracoronary imaging. *Catheter Cardiovasc Interv*. (2016) 87:E54–61. doi: 10.1002/ccd.26022

14. Jackson R, Al-Hussaini A, Joseph S, van Soest G, Wood A, Macaya F, et al. Spontaneous coronary artery dissection: pathophysiological insights from optical coherence tomography. *JACC Cardiovasc Imaging*. (2019) 12:2475–88. doi: 10.1016/j.jcmg.2019.01.015

15. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. *J Am Coll Cardiol*. (2017) 70:1148–58. doi: .org/10.1016/j.jacc.2017.06.053

16. Díez-Villanueva P, García-Guimarães M, Sanz-Ruiz R, Sabaté M, Macaya F, Roura G, et al. Prognostic implications of left ventricular systolic dysfunction in patients with spontaneous coronary artery dissection. *Eur Heart J*. (2023) 12:299–305. doi: .org/10.1093/ehjacc/zuad035

17. Mori R, Macaya F, Giacobbe F, Salinas P, Rolfo C, Porto I, et al. Clinical and angiographic features of SCAD type 4. *Int J Cardiol*. (2023) 377:22–5. doi: 10.1016/j.ijcard.2023.01.067

18. van Kranenburg M, Magro M, Thiele H, de Waha S, Eitel I, Cochet A, et al. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. *JACC Cardiovasc Imaging*. (2014) 7:953–5. doi: 10.1016/j.jcmg.2014.05.010

19. Chandrasekhar J, Thakkar J, Starovoytov A, Mayo J, Saw J. Characteristics of spontaneous coronary artery dissection on cardiac magnetic resonance imaging. *Cardiovasc Diagn Ther*. (2020) 3:636–9. doi: 10.21037/cdt.2020.02.01

20. Gaine SP, Sharma G, Tower-Rader A, Botros M, Kovell L, Parakh A, et al. Multimodality imaging in the detection of ischemic heart disease in women. *J Cardiovasc Dev Dis*. (2022) 9(10):350. doi: 10.3390/jcdd9100350

21. Gowd BMP, Heller GV, Parker MW. Stress-only SPECT myocardial perfusion imaging: a review. *J Nucl Cardiol* (2014) 21:1200–12. doi: 10.1007/s12350-014-9944-y

22. Murthy VL, Bateman TM, Beanlands RS, Berman DS, Borges-Neto S, Chareonthaitawee P, et al. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI cardiovascular council and the ASNC. *J Nucl Cardiol*. (2018) 25:269–97. doi: 10.1007/s12350-017-1110-x

23. Gan LM, Svedlund S, Wittfeldt A, Eklund C, Gao S, Matejka G, et al. Incremental value of transthoracic Doppler echocardiography-assessed coronary flow reserve in patients with suspected myocardial ischemia undergoing myocardial perfusion scintigraphy. *J Am Heart Assoc*. (2017) 6:e004875. doi: 10.1161/JAHA.116.004875

24. Hayes SN, Tweet MS, Adlam D, Kim ESH, Gulati R, Price JE, et al. Spontaneous coronary artery dissection: JACC state-of-the-art review. *J Am Coll Cardiol*. (2020) 76:961–84. doi: 10.1016/j.jacc.2020.05.084

25. Mieres J. A report of the American Society of Nuclear Cardiology Task Force on Women and Heart Disease (writing group on perfusion imaging in women). *J Nucl Cardiol*. (2003) 10:95–101. doi: 10.1067/mnc.2003.130362

26. Krljanac G, Apostolovic S, Mehmedbegovic Z, Nedeljkovic-Arsenovic O, Maksimovic R, Ilic I, et al. Chronic or changeable infarct size after spontaneous coronary artery. *Dissection*. (2023) 13:1518. doi: .org/10.3390/diagnostics13091518

27. Franco C, Starovoytov A, Heydari M, Mancini GB, Aymong E, Saw J. Changes in left ventricular function after spontaneous coronary artery dissection. *Clin Cardiol*. (2017) 40:149–54. doi: 10.1002/clc.22640

28. Cameli M. Echocardiography strain: why is it used more and more? *Eur Heart J Supplements*. (2022) 24:I38–42. doi: .org/10.1093/eurheartjsupp/suac070

29. Malagoli A, Fanti D, Albini A, Rossi A, Ribichini FL, Benfari G. Echocardiographic strain imaging in coronary artery disease the added value of a quantitative approach. *Cardiol Clin*. (2020) 38:517–26. doi: 10.1016/j.ccl.2020.06.005

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 16 January 2024
DOI 10.3389/fcvm.2024.1276521

OPEN ACCESS

EDITED BY
Turgay Celik,
Wake Forest University, United States

REVIEWED BY
Anthony Matta,
Civilians Hospital of Colmar, France
Nigussie Bogale,
Stavanger University Hospital, Norway

*CORRESPONDENCE
Aleksandra Milovančev
aleksandra.milovancev@mf.uns.ac.rs

RECEIVED 14 August 2023
ACCEPTED 02 January 2024
PUBLISHED 16 January 2024

CITATION
Petrović M, Miljković T, Ilić A, Kovačević M, Čanković M, Dabović D, Stojšić Milosavljević A, Čemerlić Maksimović S, Jaraković M, Andrić D, Golubović M, Bjelobrk M, Bjelić S, Tadić S, Slankamenac J, Apostolović S, Djurović V and Milovančev A (2024) Management and outcomes of spontaneous coronary artery dissection: a systematic review of the literature.
Front. Cardiovasc. Med. 11:1276521.
doi: 10.3389/fcvm.2024.1276521

Management and outcomes of spontaneous coronary artery dissection: a systematic review of the literature

Milovan Petrović[1,2], Tatjana Miljković[1,2], Aleksandra Ilić[1,2], Mila Kovačević[1,2], Milenko Čanković[1,2], Dragana Dabović[1,2], Anastazija Stojšić Milosavljević[1,2], Snežana Čemerlić Maksimović[2], Milana Jaraković[1,2], Dragica Andrić[1,2], Miodrag Golubović[1,2], Marija Bjelobrk[1,2], Snežana Bjelić[1,2], Snežana Tadić[1,2], Jelena Slankamenac[3], Svetlana Apostolović[4,5], Vladimir Djurović[6] and Aleksandra Milovančev[1,2]*

[1]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia, [2]Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia, [3]Faculty of Sport and Physical Education, University of Novi Sad, Novi Sad, Serbia, [4]Medical Faculty, University of Niš, Niš, Serbia, [5]Clinical Center of Niš, Cardiology Clinic, Niš, Serbia, [6]Clinic of Nephrology and Clinical Immunology, University Clinical Center of Vojvodina, Novi Sad, Serbia

Background: Contemporary management of spontaneous coronary artery dissection (SCAD) is still controversial. This systematic review of the literature aims to explore outcomes in the patients treated with conservative management vs. invasive strategy.
Methods: The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed when we extensively searched three electronic databases: PubMed, ScienceDirect, and Web of Science, for studies that compared conservative vs. invasive revascularization treatment outcomes for patients with SCAD from 2003 to 2023. The outcomes of interest were all-cause death and major adverse cardiovascular events (MACE), including acute coronary syndrome (ACS), heart failure (HF), need for additional revascularization, target vessel revascularization (TVR), SCAD recurrence, and stroke.
Results: The systematic review included 13 observational studies evaluating 1,801 patients with SCAD. The overall mean age was 49.12 +/− 3.41, and 88% were females. The overall prevalence of arterial hypertension was 33.2%, hyperlipidemia, 26.9%, smoking, 17.8%, and diabetes, 3.9%. Approximately 48.5% of the patients were diagnosed with non-ST elevated myocardial infarction (NSTEMI), 36.8% with ST elevated myocardial infarction (STEMI), 3.41% with unstable angina, 0.56% with stable angina, and 0.11% were diagnosed with various types of arrhythmias. The left anterior descending artery (LAD) was the most common culprit lesion in 51% of the patients. There were initially 65.2% of conservatively treated patients vs. 33.4% that underwent percutaneous coronary intervention (PCI) or 1.28% that underwent coronary artery bypass graft (CABG). SCAD-PCI revascularization was associated with a variable range of PCI failure. The most common complications were hematoma extension and iatrogenic dissection. SCAD-PCI revascularization frequently required three or more stents and had residual areas of dissection. The overall reported in-hospital and follow-up mortality rates were 1.2% and 1.3%, respectively. The follow-up range across studies was 7.3–75.6 months.

The authors reported variable prevalence of MACE, recurrent SCAD up to 31%, ACS up to 27.4%, TVR up to 30%, repeat revascularization up to 14.7%, UA up to 13.3%, HF up to 17.4%, and stroke up to 3%.

Conclusion: Our results highlight that conservative treatment should be the preferred method of treatment in patients with SCAD. PCI revascularization is associated with a high prevalence of periprocedural complications. SCAD poses a considerable risk of MACE, mainly associated with TVR, ACS, and recurrent SCAD.

KEYWORDS

spontaneous coronary artery dissection, treatment, invasive treatment, conservative treatment, outcomes, systematic review

1 Introduction

Spontaneous coronary artery dissection (SCAD) is a rare cause of acute coronary syndrome (ACS), typically in patients without classical cardiovascular risk factors (1). The reported incidence of SCAD varies greatly, depending on the methodology and studied cohort. Previous angiographic series have reported a prevalence of SCAD ranging from 0.10% to 0.24% (2–5). Nevertheless, the incidence of SCAD rises particularly among women diagnosed with ACS before the age of 50, exhibiting a reported prevalence of up to 24% (6). Recent studies, mainly national registries, have provided growing data on the pathophysiological features of SCAD, which is now being more recognized as a cause of ACS, particularly among young and middle-aged women. In addition, risk factors for SCAD include pregnancy and peripartum periods, multiparity (i.e., more than three births) (7, 8), fibromuscular dysplasia, connective tissue disorders, hormonal therapy, systemic inflammation, and strong mechanical and emotional stressors (9).

SCAD is defined as a non-traumatic and non-iatrogenic separation of the coronary arterial walls, creating a false lumen (10) between the intima and media or between the media and adventitia. It can potentially arise from an intimal rupture, disrupting the vessel wall, or bleeding in the vasa vasorum, leading to the formation of an intramural hematoma. The false lumen or intramural hematoma might progressively expand as a result of the pressure, leading to increased separation between the dissected layers. This separation can compress the true lumen, resulting in myocardial ischemia or infarction (11). The clinical manifestation of SCAD varies based on the severity and extent of the coronary dissection, encompassing a spectrum from no apparent symptoms to unstable angina, acute myocardial infarction, ventricular arrhythmias, and even sudden cardiac death. Given the association of SCAD with multiple diseases and conditions, it is likely that SCAD represents a diverse and heterogeneous entity (11).

Most SCADs are diagnosed by coronary angiograms. Nevertheless, angiography lacks the ability to visualize the vessel wall and exhibits restricted diagnostic accuracy. However, novel tomographic techniques such as intravascular ultrasound (IVUS), optical coherence tomography (OCT), or multislice computed tomography (MSCT) provide unprecedented diagnostic insights in specific cases (12, 13). Furthermore, MSCT has been used for longitudinal follow-up evaluation of patients with SCAD (11).

Nonetheless, contemporary management is still controversial and it represents the main focus of the research. The management and outcomes of SCAD are substantially different from atherosclerotic ACS. In particular, the question of whether conservative medical management or coronary revascularization offers more benefits and improves outcomes is still unresolved, leaving the matter open to further discussion and research (9, 14). There are no randomized clinical trials that address this research question. Still, the European Society of Cardiology position paper (1) and the American Heart Association Scientific Statement (15) on SCAD favor a conservative strategy when revascularization is not mandatory for hemodynamic instability or ongoing ischemia. This is mostly because of the suboptimal percutaneous coronary intervention (PCI) success and the high risk of peri- and postprocedural complications in the setting of SCAD noted in observational studies (1).

The aim of our systematic review of the literature is to explore outcomes in the patients treated with conservative management vs. invasive strategy.

2 Methods

Our systematic review aimed to investigate and compare outcomes of the studies reporting treatment in SCAD patients. Since SCAD is a rare disease and there is a lack of randomized clinical trials comparing treatments, the rationale behind this is the necessity to identify potential treatment recommendations.

2.1 Literature search strategy

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline was adhered to when conducting the systematic review to provide a thorough and transparent report (16). Three electronic databases, PubMed, ScienceDirect, and Web of Science, were searched extensively from 1 January 2003 to 9 May 2023,with the following keywords: "spontaneous coronary artery dissection," "SCAD," "coronary artery dissection," AND "treatment," "invasive treatment," "medical treatment," "conservative therapy," and "clinical outcomes." To find other qualified studies that did not turn up in the original search, the lists of references in the eligible articles were also examined. The

screening was carried out after the exclusion of duplicate articles. Initially, studies were excluded from the evaluation based on the title and abstract. Studies that were retained for the next phase were then screened and included if they reported any outcomes of invasive or conservative treatment of SCAD. Only articles with an available full-text version were included. Two independent investigators (SM, AM) reviewed all titles and abstracts and selected the potentially eligible ones. Any disagreements between the investigators were resolved by consensus.

2.2 Study eligibility

Studies published in the preceding 20 years were considered (with the study period defined as from 1 January 2003 to 9 May 2023). Different types of publications, including books, book reviews, editorials, comments, letters, opinion pieces, reviews, meta-analyses, abstracts from scientific conferences, and case reports were not taken into consideration. For each eligible study, full texts, supplementary materials, and online appendices were examined for inclusion/exclusion criteria.

The inclusion criteria were: original articles published in English, observational or randomized controlled trials, articles that contain or compare two techniques for SCAD treatment (conservative vs. invasive revascularization), and studies that reported outcomes. The outcomes of interest were all-cause death; cardiovascular death; and major adverse cardiovascular events (MACE): acute coronary syndrome (ACS), heart failure (HF), need for additional revascularization, target vessel revascularization (TVR), SCAD recurrence, and stroke. We excluded the following: studies contrasting the two approaches that did not provide clinical results; studies that, despite evaluation of the clinical outcomes, did not report in detail the type of treatment strategy; and studies that were considered very low quality or had inadequate methodology. The original study protocol was registered on the PROSPERO platform with ID CRD42023444058.

2.3 Data extraction

The key information about the articles included in this review is presented in tabular form (Microsoft Word 2016, Microsoft, Washington, DC, USA), while the analysis of the included literature was performed descriptively. Certain specificities of some studies that go beyond the tabular explanation are described in narrative detail in the Results section. Data regarding study design, sample size, clinical presentation, coronary angiography findings, length of follow-up, and outcomes of interest were extracted from the selected studies. The screening processes have been summarized via the PRISMA flowchart (Figure 1).

2.4 Risk of bias assessment

Two independent researchers assessed the risk of bias using the Downs and Black checklist (17). After evaluation, the studies were classified as "high quality" (scoring 23–32), "moderate quality" (score 19–22), "lower quality" (score 16–18), or "poor quality" (score lower than 15) (18). Furthermore, an average of all ratings was generated to estimate the overall quality of the included research. The study design and the Downs and Black scores were used to determine the quality of evidence. Overall, 15.4% of the studies were of poor quality, 53.8% were of low quality, and 30.8% were of moderate quality (Figure 2).

2.5 Statistical analysis

Continuous variables are expressed as means ± standard deviations or median (with interquartile range) values, and categorical variables are described as numbers and percentages. To establish inter-rater reliability between two researchers who completed the bias checklist, the interclass correlation statistical approach (SPSS, IBM, New York, USA, v.20) was employed.

3 Results

There were 134,553 records identified from databases in the literature search. After removing ineligible records, 72 titles and abstracts were screened, 50 records were removed after abstract reading, and 22 publications were thoroughly assessed according to eligibility exclusion and inclusion criteria. Finally, 13 studies were included in the analysis. All of the studies were observational, with the majority being retrospective and only a few collecting prospective data. There were no randomized clinical studies. The authors reported single-center data in 10 studies, and 3 studies (19–21) were multicentric. Across all studies, sample sizes had a median (range) of 64 (10–436), and 5 trials (38.5%) had a sample size greater than 100.

3.1 Presentation and clinical characteristics

The systematic review included 1,801 individuals, and the baseline characteristics are reported in Table 1. Sufficient overall data were available in 13 studies. The overall median age was 49.12 ± 3.41, with 88% being females. Overall prevalence of arterial hypertension was 33.2%, hyperlipidemia, 26.9%, smoking, 17.8%, and diabetes, 3.9%. Out of the total cases, 48.5% were diagnosed with non-ST elevated myocardial infarction (NSTEMI), 36.8% had ST elevated myocardial infarction (STEMI), 3.41% experienced unstable angina (UA), 0.56% had stable angina (SA), and 0.11% were diagnosed with various types of arrhythmias. The left anterior descending artery (LAD) was the most common culprit lesion in 51%, followed by the right coronary artery (RCA) in 24.3%, left circumflex coronary artery (LCX) in 28.1%, and left main coronary artery (LM) in 2.85%. The majority of patients had one vessel disease, but the authors also report multivessel disease in prevalence in up to 13% of the patients (21).

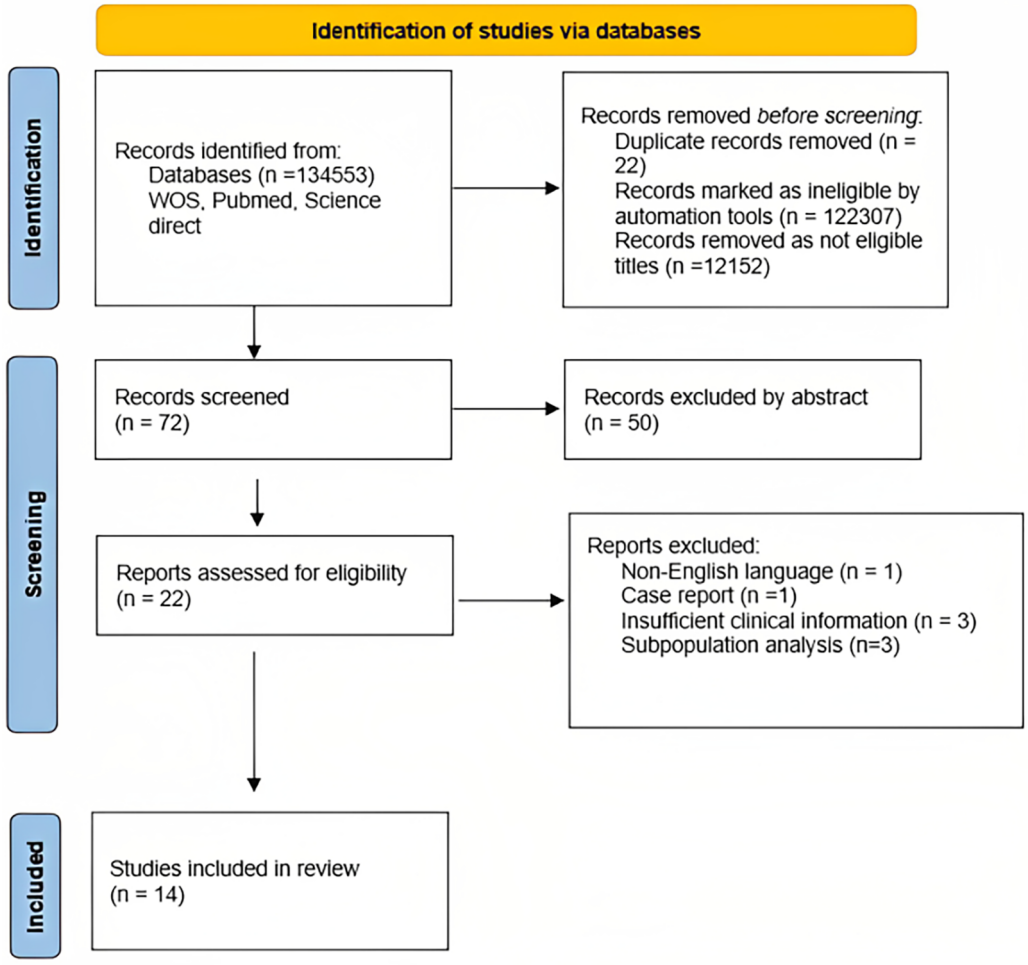


FIGURE 1
Flowchart PRISMA for management and outcomes of spontaneous coronary artery dissection: a systematic review of the literature.

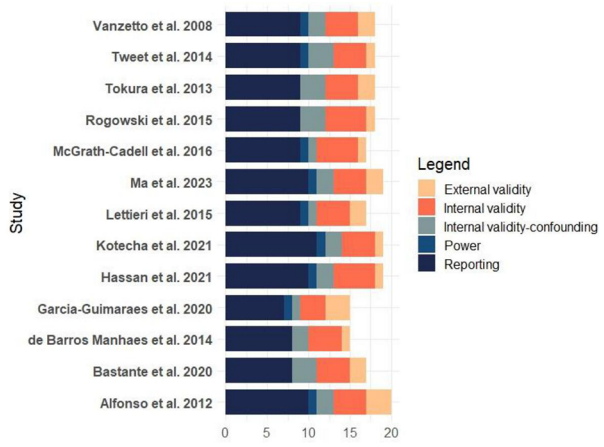


FIGURE 2
Figure one bias assessment for included studies in the systematic review: management and outcomes of spontaneous coronary artery dissection.

There were initially 65.2% of conservatively treated patients vs. 33.4% that underwent PCI or 1.28% that underwent coronary artery bypass graft (CABG). The overall rate of PCI conversion into CABG was 3.42%.

3.1 Differences between PCI vs. conservative treatment studies

The prevalence of the initial approach varies between studies. Some studies had a similar number of patients treated conservatively vs. revascularization and some favored conservative management. Vanzetto et al. (3) included 23 patients, with conservative treatment in 43% and revascularization in 57%, [CABG in 9% and percutaneous transluminal coronary angioplasty (PTCA) in 48%]. Revascularization procedures were mainly performed in patients with dissection involving theLM and the proximal or mid-LAD, while medical therapy was the preferred strategy in other

TABLE 1 Basic SCAD patients characteristics.

Author and year	*n*	*F* (%)	Age	Clinical presentation upon admission (%)					SCAD location (%)				Initial treatment (%)		
				STEMI	NSTEMI	UA	SA	Arrhythmia	LM	LAD	LCX	RCA	CON	CABG	PCI
Vanzzeto et al. (3)	23	74	46 ± 9	30.4	60.9	0	0	8.7	13	52	22	13	43	9	48
Tweet et al. (22)	189	91.5	44 ± 9	37		0	0	0	4	61	25	25	48.7	3.17	46.03
Ma et al. (23)	81	67.9	56.8	23.5	13.6	58	4.9	0	2.5	31.2	9.9	55.6	44.4	6.2	49.4
De Barros Manhaes et al. (25)	25	56	48.8 ± 10	40	40	12	8	0	7.4	48	18.6	25.9	56	4	40
Alfonso et al. (13)	45	58	53 ± 11	40	36	0	9	0	2	53	16	29	80	2.2	17.8
Kotecha et al. (19)	436	93.1	48.5	44.9	47	0	0	0	4.1	61.2	30	20	50.7	0	49.3
Lettieri et al. (27)	134	81	52 ± 11	49.2	40.3	3	0	0	2.8	36.1	14.6	27.1	58.2	3.7	38
McGrath-Cadell et al. (21)	40	95	45 ± 10	30	65	0	0	0	2.5	68	25	18	67.5	5	30
Rogowski et al. (28)	64	94	53 ± 11.2	30	69	0	0	0	4.7	45	45	10	87.5	1.6	10.9
Tokura et al. (24)	10	90	46 ± 17	90		10	0	0	0	40	10	50	10	0	90
Bastante et al. (8)	33	97	56 ± 12	27	73	0	0	0	0	51	24	24	82	0	18
Hassan et al. (29)	403	91.3	48.9 ± 10.1 53.1 ± 9.6	25.6	74.4	0	0	0	1	49.1	32.5	26.1	81.4	0	18.6
Garcia-Guimaraes et al. (20)	318	88	53 ± 13	39	53	2	0	0	2	44	33	21	78	0	22

CABG, coronary artery bypass graft; CON, conservative treatment; F, females; LAD, left anterior descending artery; LM, left main coronary artery; LCX, left circumflex coronary artery; NSTEMI, non-ST elevated myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SA, stable angina; STEMI, ST elevated myocardial infarction; UA, unstable angina.

locations. Tweet et al. (22) reported that those treated with initial revascularization more frequently presented with STEMI compared with those managed conservatively (51% vs. 23%; $p = 0.0002$) with higher rates of vessel occlusion (48% vs. 19%; $p < 0.0001$), larger vessel diameter (2.8 vs. 2.6 mm; $p = 0.011$), and higher mean lesion stenosis (90% vs. 75%; $p < 0.0001$). CABG was performed after PCI failure. Ma et al. (23) divided SCAD patients into high or low risk based on the lesion location and intramural hematoma. LM or proximal coronary artery segment involvement was categorized as high risk. PCI revascularization was the treatment strategy in 49.4%, and in 6.2% CABG was performed compared with the 44.4% managed conservatively. More patients in the high-risk group received PCI (68.4% vs. 32.5%, $p < 0.01$), while most patients in the low-risk SCAD group received conservative management (62.8% vs. 23.7%, $p < 0.01$). Kotecha et al. (19) compared the PCI vs. the conservative treatment cohort. PCI-treated SCAD patients had a higher prevalence of proximal, midvessel, and multisegment coronary artery lesions. Tokura et al. (24) included 10 patients. Thrombus aspiration alone was performed in three patients and it was suggested as one of the possible strategies in selected patients with SCAD, four patients were treated with stenting, two with balloons, and one conservatively.

The subsequent studies preferred initial conservative treatment. The study by de Barros Manhaes et al. (25) included 25 patients predominantly treated medically in 56% of the cases vs. the 40% PCI treated. Only the patient with multivessel dissection was treated with CABG. Alfonso et al. (26) divided SCAD patients into isolated SCAD (60%) and atherosclerosis-associated SCAD (40%). At diagnosis, the initial therapeutic strategy was always conservative medical management. Overall, nine patients (20%) required revascularization for ongoing ischemia at the time of diagnosis, seven were treated with stents, one, with balloon angioplasty, and one with LM SCAD required CABG. The study by Lettieri et al. (27) included 134 patients of which 58% were initially treated conservatively, and 42% underwent coronary revascularization as first-choice therapy. Two patients who were initially treated conservatively underwent subsequent revascularization because of clinical destabilization and angiographic progression of the dissection. CABG was performed for multivessel dissection or left main coronary artery involvement. McGrath-Cadell et al. (21) included 40 patients, of which 68% were managed medically, 30% had PCI, and 5% had CABG (rescue CABG following a ventricular fibrillation cardiac arrest, immediate two-vessel CABG when presenting with LAD and right coronary artery SCADs). Rogowski et al. (28) followed initial conservative strategy in 87.5% (PCI was performed in 9.4% because of impaired flow and ongoing chest pain, and after resuscitation. One urgent CABG was done for LAD and first diagonal branch occlusion). Bastante et al. (8) included 33 patients and initial conservative treatment was the first option in most cases (82%). Only six patients were treated with PCI as the initial strategy, four of them because of progressive flow worsening with contrast injections. The PCI conventional success was reported in 50% of the cases, and the PCI-SCAD success in 67% of the cases. One iatrogenic dissection was reported in the LM.

Hassan et al. (29) included 403 patients, 18.6% underwent PCI of the SCAD-affected artery, and 81.4% were treated conservatively during their initial SCAD hospitalization. Of the 75 SCAD patients who underwent PCI, 60 had PCI as their first-treatment strategy (80.0%), 11 had PCI after failed initial medical treatment (14.6%), and 4 had PCI after thrombolysis (5.3%). PCI was deemed successful in 34.7% (26/75), partially successful in 37.3% (28/75), and unsuccessful in 28.0% (21/75). The indications for PCI were ongoing ischemia, ongoing symptoms, ventricular tachycardia (VT) or ventricular fibrillation (VF), hemodynamic instability, LM dissection, large artery >33 mm, proximal segments, severe stenosis (90%–100%), TIMI 0 or 1 flow, Multivessel SCAD, catheter-induced dissection, and others. Garcia-Guimares et al. (20) included 318 patients. Most patients

were initially managed conservatively (78%). Independent predictors of adverse events were initial management with percutaneous coronary intervention (OR, 5.97; 95% CI 1.78–20, $p = 0.004$) and angiographic presentation as intramural hematoma (OR, 4.96; 95% CI 1.19–21; $p = 0.028$).

3.2 Medical therapy

Generally, in-hospital medical therapy did not differ from standard pharmacological treatment for patients with ACS. The studies that reported details about medications are narratively described. Alfonso et al. (26) reported that at discharge patients received standard of care dual antiplatelet therapy (DAPT) for up to 12 months, oral anticoagulants, beta-blockers, calcium-channel blockers, and angiotensin system antagonists. In a study by Garcıa-Guimaraes et al. (20), at discharge 92% of patients were on low-dose aspirin and more than half (59%) were on DAPT, although relatively few were on potent antiplatelet agents (ticagrelor, 19% and prasugrel, 3%). Additional treatments at the time of discharge included beta-blockers (79%), statins (79%), and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEi/ARB) (51%). Other authors (25) also reported that the pharmacological therapy was based on the combination of antithrombotic and anti-ischemic drugs. Lettieri et al. (27) reported 94% of PCI patients and 82% of medically treated patients received DAPT. Ticlopidine, clopidogrel, and a new P2Y12 receptor inhibitor were used in 6%, 87%, and 7% of the patients, respectively, whereas 6% received oral anticoagulants. DAPT was continued for 11.9 ± 7.1 months. A group of multicenter Australian authors in their multicentric study reported (21) that among medically managed patients, 78% were prescribed a beta-blocker, 89%, aspirin, 74%, an additional antiplatelet agent, 59%, an ACEi/ARB, 41%, a statin, and 7%, a calcium channel blocker. Rogowski et al. (28) reported that aspirin was prescribed in 97%, DAPT in 92%, oral anticoagulants in 6%, statin in 89%, beta-blockers in 86%, ACEi/ARB in 36%, and calcium channel blockers in 19% of the cases. Bastante et al. (8) reported prescribed ASA in 94%, clopidogrel in 27%, ticagrelor in 15%, DAPT in 42%, anticoagulation in 6%, beta-blockers in 85%, ACEi/ARB in 64%, statins in 76%, nitrates in 9%, and Ca-channel blockers in 9%.

3.3 Characteristics of SCAD revascularization

In the cohorts that were treated by PCI, variable incidences of complications were reported. Alfonso et al. (26) reported PCI-associated complications in 25% of the patients in the PCI group vs. the 2.7% of the conservative group. The catheter-induced, remote iatrogenic dissection of the vessel initially treated with stents underwent a second intervention with additional stent implantation in segments showing severe residual dissections. Venzeto et al. (3) reported PTCA failure in 27.2% of the patients with immediate or delayed (<48 h) extension of the dissection requiring emergency CABG. Tweet et al. (22) reported PCI failure occurrence in 53% overall, while when SCAD specific criteria (flow-based) were used, the failure rate was 30%. The reasons for technical failure in the PCI group with preserved vessel flow (23/46) were failure to cross the vessel with a wire or device because of wire entry into a false lumen (7/23), and final loss of flow after stent placement with residual stenosis >30%. Hassan et al. (29) reported PCI as successful in 34.7%, partially successful in 37.3%, and unsuccessful in 28%. The majority of the PCI-treated patients (73.3%) had stent implantation (5/55 were unsuccessful), angioplasty alone was performed in 16% (8/12 cases were unsuccessful), wiring alone was attempted in 10.7% (8/8 were unsuccessful), and cutting balloon was used in only one case. The mean number of stents implanted was 2.6 ± 1.8, and more than three stents were used in 15% of the cases. Of all PCI cases, propagation of SCAD occurred in 44%, and residual dissection was observed in 58.7%. Final TIMI 3 flow was observed in 72%, and improved TIMI flow with PCI occurred in 62.7%. Four patients required emergency bailout CABG (5.3%). In the study by Kotecha et al. (19) with the highest cohort of PCI patients (215), 72.6% of the patients underwent stenting, mostly with drug-eluting stents, 20.9% had balloon angioplasty, 5%, with cutting balloons, and 6.5% underwent wiring only. The mean number of stents deployed was 2.3 (range 1–8) per stented case, 10.6% of all SCAD-PCI cases required four or more stents. The median total length of deployed stents was 46 mm, with 29.8% of all SCAD-PCI cases requiring ≥50 mm stents, and 64.1% of the stented cases were left with residual unstented areas of dissection. PCI complications occurred in 38.6% of SCAD-PCI patients with the most common being hematoma extension in 27% and iatrogenic dissection in 8.4%. The total number of implanted stents emerged as a positive predictor for the risk of complications (OR = 1.90; 95% CI 1.26–2.85), and the maximum stent diameter remained associated with risk of serious complications in SCAD-PCI patients (OR = 2.62; 95% CI 1.28–5.39). Lettieri et al. (27) reported procedural success of PCI in 72.5% of the patients. Initial PCI was unsuccessful in 5.9%. In the study that included 318 patients, Garcıa-Guimaraes M et al. (20) found that the most common PCI procedures were drug-eluting stent implantation (58%), simple balloon angioplasty (15%), and bioresorbable device implantation (13%). The PCI success rate was 57% according to the conventional definition and 81% according to the SCAD-specific definition. Similar PCI conventional success (50%) was reported by Bastante et al. (8), and PCI-SCAD success was observed in 67% of the cases.

Tokura et al. (24) reported PCI protocol on 10 patients, where first aspiration thrombectomy was tried, then if sufficient blood flow was not obtained, subsequently balloon angioplasty followed, and bare metal stents were placed as the final step.

3.4 Outcomes

Short- and long-term outcomes are reported in detail in Table 2. In-hospital MACE prevalence was low. Overall reported in-hospital mortality was also low (1.2%). In-hospital mortality

TABLE 2 Outcomes and follow-up of included SCAD studies patients.

Author and year	In-hospital death (%)	In-hospital MACE (%)	Median FU time	FU mortality (%)	FU MACE (%)	Cross-over during hospitalization	Major outcomes
Vanzzeto et al. (3)	8.7	NR	15.6 months	Overall 4.5	HF: 17.4	3 PCI → CABG	1-year event-free survival was 74%
Tweet et al. (22)	0.5 REV	NR	2.3 years	Overall: 2 1 REV vs. 4 CON	Recurrent SCAD: 23 REV vs. 31 CON TVR: 30 REV vs. 19 CON HF: 12 REV vs. 16 CON	13 PCI → CABG 9 CON → CABG / PCI	PCI for SCAD is associated with significant rates of complications and urgent CABG. CABG offers excellent early outcomes for certain patients. The risk of long-term TVR or recurrent SCAD is not decreased by revascularization
Ma et al. (23)	0	NR	1 year	1.2 PCI	Overall: 12.3 UA: 5 REV (PCI) vs. 8.3 CON HF: 5.6% CON	NR	Rates of vessel healing are comparable in CON (low-risk SCAD) vs. REV (high-risk SCAD) group
De Barros Manhaes et al. (25)	0	Overall: 8 Stroke: 4 AMI: 4	75.6 ± 43.1 months	Overall 5.3	5.3 ACS	0	In-hospital MACE-free event was 92%, one patient in the CON group had stroke and one in the PCI group had recurrent AMI. In long FU, 84.2% event-free rate was reported
Alfonso et al. (26)	2.2	0	730 days	0	Overall: 6.6 (all in PCI) HF: 2.2 TVR: 4.4	7 CON → PCI 1 → CABG	At 3 years, 94% and 88% of patients in the I-SCAD and A-SCAD groups, respectively, were free of adverse events
Kotecha et al. (19)	0	NR	900 days	Overall: 0.9 (1.4 PCI vs. 0.5 CON)	Overall: 12.1 REV: PCI 14.4 vs. 9.5 CON ACS: 9.3 PCI vs. 7.7 CON TVR: 4.7 PCI vs. 1.4 CON Stroke: 1.5 PCI vs. 0.7 CON Re-SCAD: 6.1 PCI vs. 6.8 CON	2 PCI → CABG 2 CON → CABG	There was no difference in MACE events between SCAD-PCI and SCAD-non-PCI patients. Although more extensive stenting may be required, with an elevated risk of procedural complications, improved coronary flow and good medium-term outcomes can be achieved with PCI
Lettieri et al. (27)	Overall: 2.2 (1.3 CON vs. 3.6 REV)	AMI 5.2 (2.6 CON vs. 8.9 PCI)	22 months	Overall: 3.1 (2.7 CON vs. 3.8 REV)	Stent thrombosis: 2.4 REV ACS: 1.3 CON vs. 1.9 REV HF: 4 CON vs. 3.8 REV Repeated re-vascularization: 1.3 CON vs. 9.4 REV	2 CON → PCI 3 PCI → CABG 5 re-PCI→CABG	The prognosis in the short and long term in the CON and REV group is generally good, PCI procedure success was less than anticipated and case-specific treatment is manageable and safe
McGrath-Cadell et al. (21)	0	NR	16 months	0	ACS: 10 (7.5 recurrent SCAD in CON; 2.5 stent thrombosis in PCI) Coronary artery aneurysm: 5	3 PCI → CABG	13% of patients had multiple coronary areas involved. The major associated vascular condition is FMD
Rogowski et al. (28)	1.6 (PCI)	NR	4.5 years	0	ACS: 3.2 (CON) Persistent dissection:1.1 (CON)	3 CON → PCI	The long-term results are favorable with conservative treatment
Tokura et al. (24)	0	NR	7.3 months	0	Recurrent SCAD: 10	0	Regardless of the initial treatment, hospital mortality is low, but PCI is linked to a high prevalence of complications
Bastante et al. (8)	0	15 (CON)	33 months	Overall 6.1	Overall: 18 In stent restenosis 3 (PCI) Recurrent SCAD: 12 Chest pain: 9.1 ACS: 9 HF: 3 Stroke: 3	NR	Favorable outcomes were observed in CON vs. PCI. In CON, utilizing a low-intensity antithrombotic strategy using only ASA, and for a limited duration, appears to yield favorable outcomes
Hassan et al. (29)	0.3	Overall: 29.3 PCI vs. 2.8 CON	3.7 years	1.2 non-PCI	Overall: 58.7 (PCI) vs. 22.6 CON	11 CON → PCI	In comparison with conservative therapy, PCI was linked to worse

(*Continued*)

TABLE 2 Continued

Author and year	In-hospital death (%)	In-hospital MACE (%)	Median FU time	FU mortality (%)	FU MACE (%)	Cross-over during hospitalization	Major outcomes
		AMI: 20 PCI vs. 1.2 CON Re-revascularization: 18.7 PCI vs. 0.9 CON CVA: 4 PCI vs. 0.6 CON			Post-discharge MACE: 24 PCI vs.19.8 CON UA: 13.3 PCI vs. 5.8 CON Recurrent AMI: 17 PCI vs. 18 CON Recurrent *de novo* SCAD: 6.7 PCI vs. 12.2 CON Repeat revascularization: 14.7 PCI vs. 3 CON CVA: 1.3 PCI vs. 1.2 CON		procedural success, increased hospital complications from recurrent MI, repeat revascularization, and stroke, as well as long-term risk from repeat revascularization
Garcia-Guimaraes et al. (20)	Overall 1.3	Reinfarction: 3 Unplanned revascularization: 4 Stroke: 1 HF: 1	NR	NR	TVR: 1.3	8 CON → PCI	Most patients were initially treated with a conservative approach and survival rates from admission to discharge were excellent. Outcomes of PCI as first-line therapy were suboptimal

CON, conservative treatment group; REV, revascularization group; PCI, percutaneous coronary intervention; TVR, target vessel revascularization; CABG, coronary artery bypass grafting; A-SCAD, SCAD associated with coronary artery disease; I-SCAD, "Isolated" SCAD; MACE, major adverse cardiovascular event; AMI, acute myocardial infarction; ACS, acute coronary syndrome; FMD, fibromuscular dysplasia; IMH, intramural hematoma; HF, heart failure; CVA, cerebrovascular accident; ASA, acetylsalicylic acid; LM, left main coronary artery; LAD, left anterior descending artery; NR, not reported.

was reported in both groups in 12 studies, in total eight deaths in the conservative treatment group and seven in the revascularization group; the others did not classify mortality based on the treatment group. The follow-up (FU) range across studies was 7.3–75.6 months. Median mortality rate in FU was 1.3% (2.7% conservative vs. 2.5% revascularization group). Event-free follow-up MACE was high from 74% to 94%. The authors reported variable prevalence of follow-up MACE, recurrent SCAD up to 31%, ACS up to 27.4%, TVR up to 30%, repeated revascularization up to 14.7%, UA up to 13.3%, HF up to 17.4%, and stroke up to 3%. It is possible to explain the variation in the occurrence of MACE in different studies based on the number of patients included and the initial treatment approach. The observational nature of some studies could lead to selection bias and result in varying frequencies of MACE. Nevertheless, studies that included the highest number of patients treated with PCI overall showed a higher prevalence of MACE. In addition, in studies with the highest number of included patients (20, 29), PCI was deemed as suboptimal. The general conclusion in the majority of included studies is that conservative treatment should be the preferred method of treatment. In studies that did report follow-up angiographies, a high prevalence of vessel healing in bout groups was observed (23).

4 Discussion

Our systematic review of the literature tried to explore outcomes in patients diagnosed with SCAD treated with either conservative management or invasive strategy. Generally, authors reported that revascularization with PCI is associated with a higher prevalence of complications. Overall short- and long-term mortality is low and irrelevant to treatment strategy. Furthermore, event-free rate for follow-up is high. The most often reported MACE in FU was TVR, recurrent SCAD, and ACS. CABG offers excellent results in particular cases.

4.1 SCAD population characteristics

In our systematic report overall, median age was 49.12 +/− 3.41, with 88% being females. Our results are complementary with other systematic reviews and meta-analyses (9, 14, 30) that reported that SCAD primarily affects young- to middle-aged women. Although there are limited data available on SCAD due to its rarity, studies have consistently shown that women, particularly those between the ages of 30 and 50 years, represent the majority of the cases. However, it is important to note that SCAD can affect people of any age and gender. The age range of reported SCAD cases extends from 18 to 84 years, highlighting the variability in its occurrence. The reasons behind the higher prevalence of SCAD in young- to middle-aged women are still not fully understood. Some potential contributing factors include hormonal changes, such as those occurring during pregnancy or in the postpartum period, as well as underlying connective tissue disorders. Emotional stress and extreme physical exertion have also been implicated as potential triggers for SCAD in some cases. We observed a low prevalence of traditional atherosclerotic risk factors in studies included in our review. Our results were very similar to Clare et al. who compared a cohort of 208 SCAD patients with other patients presenting with ACS and found much lower prevalence of atherosclerotic risk factors, as follows:

hypertension (30.8% vs. 64.8%), hyperlipidemia (27.9% vs. 62.2%), obesity (18.7% vs. 21.1%), diabetes mellitus (8.2% vs. 35.6%), and chronic kidney disease (4.3% vs. 24.3%). It is known that SCAD patients have fewer traditional risk factors (22). Nonetheless, contrary to the prior understanding, many patients do pose risk factors for ischemic heart disease, such as hypertension, smoking, and dyslipidemia, though there is no firm evidence that these contribute directly to the increased risk of SCAD (1).

In patients presenting with ACS, SCAD is generally rare, approximately noted to occur in 3%–4% (13). Among women presenting with ACS, the prevalence was reported to be higher, at 8.7% in those under 50 years old (3). Some authors reported a much higher prevalence of 24% (10) and 35% (31) in women <50 years after reviewing angiographies, thus highlighting that diagnosis can be often missed. The clinical presentation of patients with SCAD can vary widely. In our systematic review, the majority of patients, 84%, presented with ACS, with a higher prevalence of NSTEMI, compared with STEMI. In two previous studies, it was found that a greater proportion of patients with SCAD presented with STEMI ranging from 80% to 84%, in contrast to NSTEMI, which accounted for only 8%–16% of cases, while 4% of patients presented with UA (32, 33). The reason could be a lower prevalence of angiographies in NSTEMI in the previous reports. In various series, the reported prevalence of SCAD cases presenting with STEMI range from 26% to 87%, in addition, 13%–69% of SCAD patients present with NSTEMI (10, 27, 28, 31). Chest pain is usually the most commonly reported symptom (24) in 95% of the cases (15), though there are reported cases of shock (3) and sudden cardiac death (24). Nearly half of the patients with SCAD commonly had the LAD identified as the most frequent culprit lesion in our report. Similar observations have been reported in other study groups as well (34, 35).

4.2 SCAD prognosis and treatment

In recent years, there has been a notable rise in the diagnosis of SCAD owing to the increased awareness among cardiologists and the advancements in intracoronary imaging techniques. Nevertheless, optimal SCAD treatment is still debated because of the lack of large-series registries and randomized trials. The mechanism of vessel obstruction, the acute response of the blood vessel to balloon dilation, and the natural progression of conservatively managed lesions exhibit notable differences between SCAD and atherosclerotic ACS. In SCAD, vessel obstruction occurs as a result of a tear or separation within the layers of the coronary artery wall, forming a false lumen. This mechanism differs from the gradual buildup of plaque seen in atherosclerosis, which is the primary cause of vessel obstruction in ACS of an atherosclerotic origin. When it comes to the acute response of the blood vessel during balloon dilation, SCAD and atherosclerotic ACS again display dissimilarities. The characteristics of the affected vessel, such as its fragility and susceptibility to further dissection, influence the response to balloon dilation in SCAD cases. On the other hand, in atherosclerotic ACS, balloon dilation is typically employed to address the plaque and restore blood flow through the narrowed artery. Furthermore, the natural history of conservatively managed lesions also varies between SCAD and atherosclerotic ACS. SCAD lesions may exhibit a propensity for spontaneous healing and resolution over time in 70%–97% (22, 28, 36) of the selectively restudied patients after a conservatively managed index episode, whereas atherosclerotic lesions often require long-term medical management to prevent disease progression and subsequent complications. Angiographic healing is usually observed within a month (15).

The summarized data in our study suggest that conservative treatment should be absolutely preferred for patients with SCAD. In addition to this, the existing evidence strongly supports (7, 15) the adoption of a conservative approach in the majority of cases, reserving PCI with stent implantation only for unstable patients with compromised distal flow and evident ongoing ischemia. In conservatively treated patients, adverse events are usually seen in the first 7 days, hence intensive monitoring is recommended during this time. There is substantial evidence that the majority of SCAD cases tend to stabilize and eventually heal entirely over time when managed conservatively (1).

Thrombolysis is not recommended for the immediate treatment of SCAD, anticoagulants are also not recommended in routine use (1). The use and duration of antiplatelet therapies for SCAD patients are subjects of debate and vary among reported studies. As there are no randomized trials that investigate the risks and benefits of particular pharmacological treatments, recommendations are based on observational studies and available data. For patients who undergo stenting, current ACS guidelines suggest dual antiplatelet therapy for 12 months, followed by prolonged or lifelong monotherapy (usually with low-dose aspirin). Many experts support the use of acute DAPT during the initial phase, typically involving aspirin and clopidogrel rather than newer P2Y12 inhibitors while avoiding intravenous antiplatelet therapies (15). While DAPT has been widely used in SCAD, there is some registry evidence that DAPT in conservatively treated patients is associated with a significantly higher incidence of MACE when compared with single antiplatelet therapy. DAPT has been prescribed for 12 months in almost all cases (37).

Currently, a prescription of beta-blocker in SCAD is considered for left ventricular dysfunction, arrhythmias, or other indications in SCAD patients (15). Nonetheless, Saw et al. (6) reported that beta-blockers appeared to be protective in long-term cardiovascular events. As there are no randomized controlled trials to support the evidence of different treatment regimes in SCAD, the newly released Scientific Statement of the American Heart Association strongly endorsed the need for multidisciplinary and international trials for SCAD treatment. Alfonso et al. (38) published a protocol of randomized trial that will assess the efficacy and safety of different antiplatelet and beta-blocker regimes for SCAD patients. It is expected that the study will be finished in September 2024. Statins are not routinely advised for SCAD patients. There was conflicting evidence of statin safety and efficiency in SCAD (38). Decisions on other pharmacological regime prescriptions like AC inhibitors should be guideline based

and individualized (1). Overall, the management of SCAD patients involves complex decisions and may vary based on individual circumstances and guidelines.

4.3 Outcomes

Our study reports low in-hospital and long-term mortality, of 1.2% and 1.3% retrospectively, on 1,801 SCAD patients. Bocchino et al. reported all-cause deaths in 2.9% of patients in the medical treatment group and 4.8% of patients in the revascularization group during a mean follow-up of 28 ± 14 months, without significant differences pooled from 24 studies. In addition to these, meta-analysis reported mortality rates without statistical difference between the two treatment approaches (14). SCAD-associated ACS is linked to a more favorable prognosis compared with atherosclerotic coronary artery disease (35). Nevertheless, we reported that SCAD poses a significant risk of MACE, mainly associated with TVR, ACS, and recurrent SCAD. Similar results are also reported by Martins et al. (14), where a significantly higher risk of TVR was found in the PCI-treated group. Recurrence of SCAD is also widely observed (9).

5 Conclusion

The aggregated information within our study indicates that SCAD is more prevalent among females with a low occurrence of traditional atherosclerotic risk factors. This systematic search review provided summarized data from similar studies that compared treatment strategies and outcomes. Our findings suggest that conservative treatment should be absolutely preferred in patients with SCAD, as PCI revascularization is linked to a higher prevalence of periprocedural complications. Revascularization benefits are not widely confirmed, thus it should be the treatment option for high-risk patients with hemodynamic instability, ongoing ischemia, and LM artery involvement. The medical approach to treating SCAD involves using beta-blockers if there are no contraindications, considering DAPT for a duration that ranges from 1 to 12 months (which remains a subject of debate), prescribing statins if atherosclerosis is present, and avoiding anticoagulants that could potentially worsen the expansion of an intramural hematoma (the primary cause of ischemia-induced SCAD). The overall short- and long-term mortality rates for SCAD are generally low and independent of the treatment strategy. Expected MACE prevalence is high in the SCAD population and it is reported in up to one third of patients with TVR, recurrent SCAD and ACS being the most frequent events. These findings could help us derive clinical decisions on a daily basis, likely reducing morbidity and mortality in this rare disease.

Author contributions

MP: Writing—original draft, Conceptualization. TM: Writing—original draft, Investigation. AI: Investigation, Writing—original draft. MK: Investigation, Data curation, Writing—original draft. MČ: Methodology, Writing—review & editing. DD: Investigation, Writing—review & editing. ASM: Investigation, Supervision, Writing—review & editing. SCM: Investigation, Writing—original draft. MJ: Methodology, Writing—review & editing. DA: Methodology, Writing—review & editing. MG: Validation, Writing—review & editing. MB: Validation, Writing—review & editing. SB: Validation, Writing—review & editing. ST: Supervision, Writing—review & editing. JS: Methodology, Writing—original draft. SA: Supervision, Writing—review & editing. VDJ: Formal Analysis, Writing—original draft. AM: Writing—original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Adlam D, Alfonso F, Maas A, Vrints C, Writing Committee. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J.* (2018) 39(36):3353–68. doi: 10.1093/eurheartj/ehy080

2. Ahmed MA, Hamra M, Ali M, Abdullah AS, Arnous S, Kiernan TJ. Spontaneous coronary artery dissection, challenges of diagnosis and management. *Futur Cardiol.* (2017) 13(6):539–49. doi: 10.2217/fca-2017-0050

3. Vanzetto G, Berger-Coz E, Barone-Rochette G, Chavanon O, Bouvaist H, Hacini R, et al. Prevalence, therapeutic management and medium-term prognosis of spontaneous coronary artery dissection: results from a database of 11,605 patients. *Eur J Cardiothorac Surg.* (2009) 35(2):250–4. doi: 10.1016/j.ejcts.2008.10.023

4. Tsimikas S, Giordano FJ, Tarazi RY, Beyer RW. Spontaneous coronary artery dissection in patients with renal transplantation. *J Invasive Cardiol.* (1999) 11 (5):316–21.

5. Hering D, Piper C, Hohmann C, Schultheiss HP, Horstkotte D. Prospective study of the incidence, pathogenesis and therapy of spontaneous, by coronary angiography diagnosed coronary artery dissection. *Z Kardiol*. (1998) 87(12):961–70. doi: 10.1007/s003920050253

6. Saw J, Starovoytov A, Aymong E, Inohara T, Alfadhel M, McAlister C, et al. Canadian spontaneous coronary artery dissection cohort study: 3-year outcomes. *J Am Coll Cardiol*. (2022) 80(17):1585–97. doi: 10.1016/j.jacc.2022.08.759

7. Motreff P, Souteyrand G, Dauphin C, Eschalier R, Cassagnes J, Lusson JR. Management of spontaneous coronary artery dissection: review of the literature and discussion based on a series of 12 young women with acute coronary syndrome. *Cardiology*. (2010) 115(1):10–8. doi: 10.1159/000244608

8. Bastante T, Garcia-Guimaraes M, Muniz M, Cuesta J, Rivero F, Antuna P, et al. Contemporary management of spontaneous coronary dissection. *REC-Interv Cardiol*. (2020) 2(4):247–55. doi: 10.24875/RECICE.M20000096

9. Bocchino PP, Angelini F, Franchin L, D'Ascenzo F, Fortuni F, De Filippo O, et al. Invasive versus conservative management in spontaneous coronary artery dissection: a meta-analysis and meta-regression study. *Hellenic J Cardiol*. (2021) 62(4):297–303. doi: 10.1016/j.hjc.2021.02.013

10. Saw J. Spontaneous coronary artery dissection. *Can J Cardiol*. (2013) 29 (9):1027–33. doi: 10.1016/j.cjca.2012.12.018

11. Vrints CJM. Spontaneous coronary artery dissection. *Heart*. (2010) 96 (10):801–8. doi: 10.1136/hrt.2008.162073

12. Maehara A, Mintz GS, Castagna MT, Pichard AD, Satler LF, Waksman R, et al. Intravascular ultrasound assessment of spontaneous coronary artery dissection. *Am J Cardiol*. (2002) 89(4):466–8. doi: 10.1016/S0002-9149(01)02272-X

13. Alfonso F, Paulo M, Gonzalo N, Dutary J, Jimenez-Quevedo P, Lennie V, et al. Diagnosis of spontaneous coronary artery dissection by optical coherence tomography. *J Am Coll Cardiol*. (2012) 59(12):1073–9. doi: 10.1016/j.jacc.2011.08.082

14. Martins JL, Afreixo V, Santos L, Costa M, Santos J, Goncalves L. Medical treatment or revascularisation as the best approach for spontaneous coronary artery dissection: a systematic review and meta-analysis. *Eur Heart J-Acute Cardiovasc Care*. (2018) 7(7):614–23. doi: 10.1177/2048872617706502

15. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation*. (2018) 137(19): e523–57. doi: 10.1161/CIR.0000000000000564

16. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J*. (2021) 372:n71. doi: 10.1136/bmj.n71

17. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. (1998) 52(6):377–84. doi: 10.1136/jech.52.6.377

18. Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. *Int J Behav Nutr Phys Act*. (2011) 8:98. doi: 10.1186/1479-5868-8-98

19. Kotecha D, Garcia-Guimaraes M, Premawardhana D, Pellegrini D, Oliver-Williams C, Bountziouka V, et al. Risks and benefits of percutaneous coronary intervention in spontaneous coronary artery dissection. *Heart*. (2021) 107 (17):1398–406. doi: 10.1136/heartjnl-2020-318914

20. Garcia-Guimaraes M, Bastante T, Macaya F, Roura G, Sanz R, Barahona Alvarado JC, et al. Spontaneous coronary artery dissection in Spain: clinical and angiographic characteristics, management, and in-hospital events. *Rev Esp Cardiol*. (2021) 74(1):15–23. doi: 10.1016/j.recesp.2020.02.008

21. McGrath-Cadell L, McKenzie P, Emmanuel S, Muller DWM, Graham RM, Holloway CJ. Outcomes of patients with spontaneous coronary artery dissection. *Open Heart*. (2016) 3(2):e000491. doi: 10.1136/openhrt-2016-000491

22. Tweet MS, Eleid MF, Best PJM, Lennon RJ, Lerman A, Rihal CS, et al. Spontaneous coronary artery dissection revascularization versus conservative therapy. *Circ-Cardiovasc Interv*. (2014) 7(6):777–86. doi: 10.1161/CIRCINTERVENTIONS.114.001659

23. Ma Y, Zhong X, Yin J, Lu H, Pan C, Huang D, et al. Treatment strategy for spontaneous coronary artery dissection based on anatomical characteristics. *Eur J Med Res*. (2023) 28(1):29. doi: 10.1186/s40001-023-00986-y

24. Tokura M, Taguchi I, Kageyama M, Nasuno T, Nishiyama Y, Koshiji N, et al. Clinical features of spontaneous coronary artery dissection. *J Cardiol*. (2014) 63 (2):119–22. doi: 10.1016/j.jjcc.2013.07.001

25. de Barros Manhaes E, Gomes WF, Bezerra CG, Horta PE, da Gama MN, Cesar LAM, et al. Spontaneous coronary artery dissection: therapeutic approach and outcomes of a consecutive series of cases. *Rev Bras Cardiol Invasiva*. (2014) 22 (1):32–5. doi: 10.1016/S2214-1235(15)30176-9

26. Alfonso F, Paulo M, Lennie V, Dutary J, Bernardo E, Jiménez-Quevedo P, et al. Spontaneous coronary artery dissection: long-term follow-up of a large series of patients prospectively managed with a "conservative" therapeutic strategy. *JACC Cardiovasc Interv*. (2012) 5(10):1062–70. doi: 10.1016/j.jcin.2012.06.014

27. Lettieri C, Zavalloni D, Rossini R, Morici N, Ettori F, Leonzi O, et al. Management and long-term prognosis of spontaneous coronary artery dissection. *Am J Cardiol*. (2015) 116(1):66–73. doi: 10.1016/j.amjcard.2015.03.039

28. Rogowski S, Maeder MT, Weilenmann D, Haager PK, Ammann P, Rohner F, et al. Spontaneous coronary artery dissection: angiographic follow-up and long-term clinical outcome in a predominantly medically treated population. *Catheter Cardiovasc Interv*. (2017) 89(1):59–68. doi: 10.1002/ccd.26383

29. Hassan S, Samuel R, Starovoytov A, Lee C, Aymong E, Saw J. Outcomes of percutaneous coronary intervention in patients with spontaneous coronary artery dissection. *J Interv Cardiol*. (2021) 2021:6686230. doi: 10.1155/2021/6686230

30. Chen S, Merchant M, Mahrer KN, Lundstrom RJ, Naderi S, Goh AC. Spontaneous coronary artery dissection: clinical characteristics, management, and outcomes in a racially and ethnically diverse community-based cohort. *Perm J*. (2019) 23:18.278. doi: 10.7812/TPP/18.278

31. Nakashima T, Noguchi T, Haruta S, Yamamoto Y, Oshima S, Nakao K, et al. Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: a report from the angina pectoris-myocardial infarction multicenter investigators in Japan. *Int J Cardiol*. (2016) 207:341–8. doi: 10.1016/j.ijcard.2016.01.188

32. Mortensen KH, Thuesen L, Kristensen IB, Christiansen EH. Spontaneous coronary artery dissection: a Western Denmark Heart Registry study. *Catheter Cardiovasc Interv*. (2009) 74(5):710–7. doi: 10.1002/ccd.22115

33. Olin JW, Froehlich J, Gu X, Bacharach JM, Eagle K, Gray BH, et al. The United States registry for fibromuscular dysplasia: results in the first 447 patients. *Circulation*. (2012) 125(25):3182–90. doi: 10.1161/CIRCULATIONAHA.112.091223

34. Chen S, Merchant M, Mahrer KN, Ambrosy AP, Lundstrom RJ, Naderi S. Pregnancy-associated spontaneous coronary artery dissection: clinical characteristics, outcomes, and risk during subsequent pregnancy. *J Invasive Cardiol*. (2021) 33(6): E457–66.

35. Clare R, Duan L, Phan D, Moore N, Jorgensen M, Ichiuji A, et al. Characteristics and clinical outcomes of patients with spontaneous coronary artery dissection. *J Am Heart Assoc*. (2019) 8(10):e012570. doi: 10.1161/JAHA.119.012570

36. Rashid HNZ, Wong DTL, Wijesekera H, Gutman SJ, Shanmugam VB, Gulati R, et al. Incidence and characterisation of spontaneous coronary artery dissection as a cause of acute coronary syndrome—a single-centre Australian experience. *Int J Cardiol*. (2016) 202:336–8. doi: 10.1016/j.ijcard.2015.09.072

37. Cerrato E, Giacobbe F, Quadri G, Macaya F, Bianco M, Mori R, et al. Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry. *Eur Heart J*. (2021) 42 (33):3161–71. doi: 10.1093/eurheartj/ehab372

38. Alfonso F, de la Torre Hernández JM, Ibáñez B, Sabaté M, Pan M, Gulati R, et al. Rationale and design of the BA-SCAD (beta-blockers and antiplatelet agents in patients with spontaneous coronary artery dissection) randomized clinical trial. *Rev Esp Cardiol (Engl Ed)*. (2022) 75(6):515–22. doi: 10.1016/j.recesp.2021.08.002

frontiers | Frontiers in Cardiovascular Medicine

TYPE Review
PUBLISHED 08 February 2024
DOI 10.3389/fcvm.2024.1277604

OPEN ACCESS

EDITED BY
Tommaso Gori,
Johannes Gutenberg University Mainz, Germany

REVIEWED BY
Lilia M. M. Sierra-Galan,
The American British Cowdray Medical Center, Mexico
Roberta Montisci,
University of Cagliari, Italy

*CORRESPONDENCE
Jelena Milošević
jelena.milosevic95@gmail.com

RECEIVED 14 August 2023
ACCEPTED 25 January 2024
PUBLISHED 08 February 2024

CITATION
Apostolović S, Ignjatović A, Stanojević D, Radojković DD, Nikolić M, Milošević J, Filipović T, Kostić K, Miljković I, Djoković A, Krljanac G, Mehmedbegović Z, Ilić I, Aleksandrić S and Paradies V (2024) Spontaneous coronary artery dissection in women in the generative period: clinical characteristics, treatment, and outcome—a systematic review and meta-analysis. Front. Cardiovasc. Med. 11:1277604. doi: 10.3389/fcvm.2024.1277604

Spontaneous coronary artery dissection in women in the generative period: clinical characteristics, treatment, and outcome—a systematic review and meta-analysis

Svetlana Apostolović[1,2], Aleksandra Ignjatović[2], Dragana Stanojević[1], Danijela Djordjević Radojković[1,2], Miroslav Nikolić[1], Jelena Milošević[1]*, Tamara Filipović[2], Katarina Kostić[1], Ivana Miljković[1], Aleksandra Djoković[3,4], Gordana Krljanac[4,5], Zlatko Mehmedbegović[4,5], Ivan Ilić[4,6], Srdjan Aleksandrić[4,5] and Valeria Paradies[7]

[1]Clinic for Cardiology, University Clinical Center Nis, Nis, Serbia, [2]Medical Faculty, University of Nis, Nis, Serbia, [3]Department of Cardiology, Clinical Hospital Bežanijska Kosa, Belgrade, Serbia, [4]Medical Faculty, University of Belgrade, Belgrade, Serbia, [5]Clinic of Cardiology, University Clinical Center of Serbia, Belgrade, Serbia, [6]Department of Cardiology, Institute for Cardiovascular Diseases Dedinje, Belgrade, Serbia, [7]Department of Cardiology, Maasstad Hospital, Rotterdam, Netherlands

Introduction: Spontaneous coronary artery dissection (SCAD) is a non-traumatic and non-iatrogenic separation of the coronary arterial wall.
Materials and methods: This systematic review and meta-analysis is reported following the PRISMA guidelines and is registered in the PROSPERO database. A literature search was focused on female patients in generative period (16–55 of age) with acute coronary syndrome (ACS) caused by SCAD, and comparison from that database NP-SCAD (spontaneous coronary artery dissection in non pregnant women) and P-SCAD (spontaneous coronary artery dissection in pregnant women).
Results: 14 studies with 2,145 females in the generative period with ACS caused by SCAD were analyzed. The median age was 41 years (33.4–52.3 years). The most common risk factor was previous smoking history in 24.9% cases. The most common clinical presentation of ACS was STEMI in 47.4%. Conservative treatment was reported in 41.1%. PCI was performed in 32.7%, and 3.8% of patients had CABG surgery. LAD was the most frequently affected (50.5%). The prevalence of composite clinical outcomes including mortality, non-fatal MI and recurrent SCAD was 3.3% (95% CI: 1.4–5.1), 37.7% (95% CI: 1.9–73.4) and 15.2% (95% CI: 9.1–21.3) of patients. P-SCAD compared to NP-SCAD patients more frequently had STEMI (OR = 3.16; 95% CI: 2.30–4.34; I^2 = 64%); with the left main and LAD more frequently affected [(OR = 14.34; 95% CI: 7.71–26.67; I^2 = 54%) and (OR = 1.57; 95% CI: 1.06–2.32; I^2 = 23%)]; P-SCAD patients more frequently underwent CABG surgery (OR = 6.29; 95% CI: 4.08–9.70; I^2 = 0%). NP-SCAD compared to P-SCAD patients were more frequently treated conservatevly (OR = 0.61; 95% CI: 0.37–0.98; I^2 = 0%). In P-SCAD compared to NP-SCAD mortality rates (OR = 1.13; 95% CI: 0.06–21.16; I^2 = not applicable) and reccurence of coronary artery dissection (OR = 2.54; 95% CI: 0.97–6.61; I^2 = 0%) were not more prevalent.

Conclusion: The results of this meta-analysis indicated that patients with P-SCAD more frequently had STEMI, and events more frequently involved left main and LAD compared to NP-SCAD patients. Women with NP-SCAD were significantly more often treated conservatively compared to P-SCAD patients. P-SCAD compared to NP-SCAD patients did not have significantly higher mortality rates or recurrent coronary dissection.

KEYWORDS

spontaneous coronary artery dissection, pregnancy, female population in the generative period, treatment, outcome

1 Introduction

Spontaneous coronary artery dissection (SCAD) is a non-traumatic and non-iatrogenic separation of the coronary arterial wall and an infrequent cause of acute myocardial infarction. It is more common in younger females than in other general population groups. Potential predisposing factors include fibromuscular dysplasia (FMD), partum and postpartum period, multi-parity (≥4 births), connective tissue disorders, systemic inflammatory conditions, mental stress and hormonal therapy. While uncommon, SCAD should be considered in any young patient, especially young women without a history of coronary heart disease or traditional risk factors, who presents with an acute myocardial infarction or cardiac arrest (1, 2).

Two potential mechanisms for spontaneous coronary artery dissection were described: the intimal tear hypothesis and the medial hemorrhage hypothesis. Once the SCAD happens, due to weakness of the arterial wall, dissection can further propagate anterograde and retrograde (3).

Although SCAD is most often observed in women's reproductive period, it is not yet clear whether there are differences in clinical presentation, treatment, and outcomes in pregnant women or soon after delivery, compared to other women in reproductive period. The high progesterone level during pregnancy is usually associated with SCAD because of its role in the fragility of the arterial media through the replacement of the elastic fiber and mucopolysaccharide substances and in the reduction of collagen synthesis (4, 5). Hemodynamic changes during pregnancy can also provoke SCAD. The increased cardiac output and circulatory volume during pregnancy can cause structural changes in the aorta, which can also expand to the coronary arteries (6). Some studies reported that hormonal changes with lactation may compound the effects of pregnancy (7). In patients with SCAD history, there is a risk of SCAD recurrence during pregnancy or postpartum (8).

Early diagnosis of SCAD is important because the management of SCAD differs from the atherosclerotic disease. Urgent coronary angiography is the first-line imaging for patients presenting with acute coronary syndrome (ACS). However, coronary angiography has significant limitations in diagnosing SCAD because it does not show the structure of the arterial wall. Optical coherent tomography (OCT) and intravascular ultrasound (IVUS) that image the arterial wall layers may provide further information and improve SCAD diagnosis. Still, it is not widely available and is associated with additional risks and costs (1).

The optimal management of SCAD is still unknown. All recommendations are based on expert opinions on treating individual and serial cases of SCAD. Nowadays, progress in the field of SCAD is being made by the National Registries of SCAD cases with detailed risk factors, diagnostic procedures, and treatment recommendations. This meta-analysis aims to provide a comprehensive contemporary update of SCAD assisting healthcare professionals in recognizing and managing these patients promptly and effectively. A special effort is put into detailed analysis and comparison of risk factors, coronary angiography findings, treatment, and prognosis between pregnant females with SCAD (including the three months after delivery—postpartum), labelled as P-SCAD and non-pregnant females with SCAD, labelled as NP-SCAD to facilitate early diagnostics during pregnancy or even before pregnancy in vulnerable women.

2 Material and methods

This systematic review and meta-analysis is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (9) and is registered in the PROSPERO database (CRD42023424806).

2.1 Inclusion criteria

This study included the SCAD female population in the generative period.

Inclusion criteria were: (1) females in the generative period (16–55 years) with acute myocardial infarction (AMI) caused by SCAD occurring during pregnancy or within three months post-partum; (2) the diagnosis of SCAD confirmed by coronary angiography (10), (4) for analysis we included observational studies, randomized controlled trials, quasi-randomized controlled trials, non-randomized controlled trials, prospective and retrospective cohort studies.

Studies were excluded if: (1) postmenopausal women patients were included; (2) a male population was included and not reported subgroup analysis by gender; (3) case reports and literature reviews; (4) studies that investigated only iatrogenic

coronary artery dissections; and (5) individual case series included in literature reviews were excluded to avoid double counting of results, as were restatements of prior studies that contained duplicative results.

2.2 Study selection

Two reviewers independently conducted searches on all information sources. The comprehensive search and selection process was ensured by using Rayyan QCRI software (https://rayyan.qcri.org). The comprehensive search and selection process was ensured using Rayyan QCRI software. A third reviewer (SA) identified and removed duplicates and ensured independent review of titles and abstracts by blinding decisions.

In the first step of selection, the title and abstract were examined, and in the next step, when necessary, the full articles were obtained and read. Additional studies were identified through reference and citation tracking. Only articles in English were screened. Four reviewers independently screened the title, abstract and full text. Disagreement about including studies was resolved by discussion and consensus between the reviewers and collaborators (SA, AI). The study inclusion process is presented using the PRISMA flowchart (Figure 1).

2.3 Search strategy

We comprehensively searched electronic databases, including MEDLINE and Mendeley, limited to English-language publications. The initial search was performed on 04 April 2023

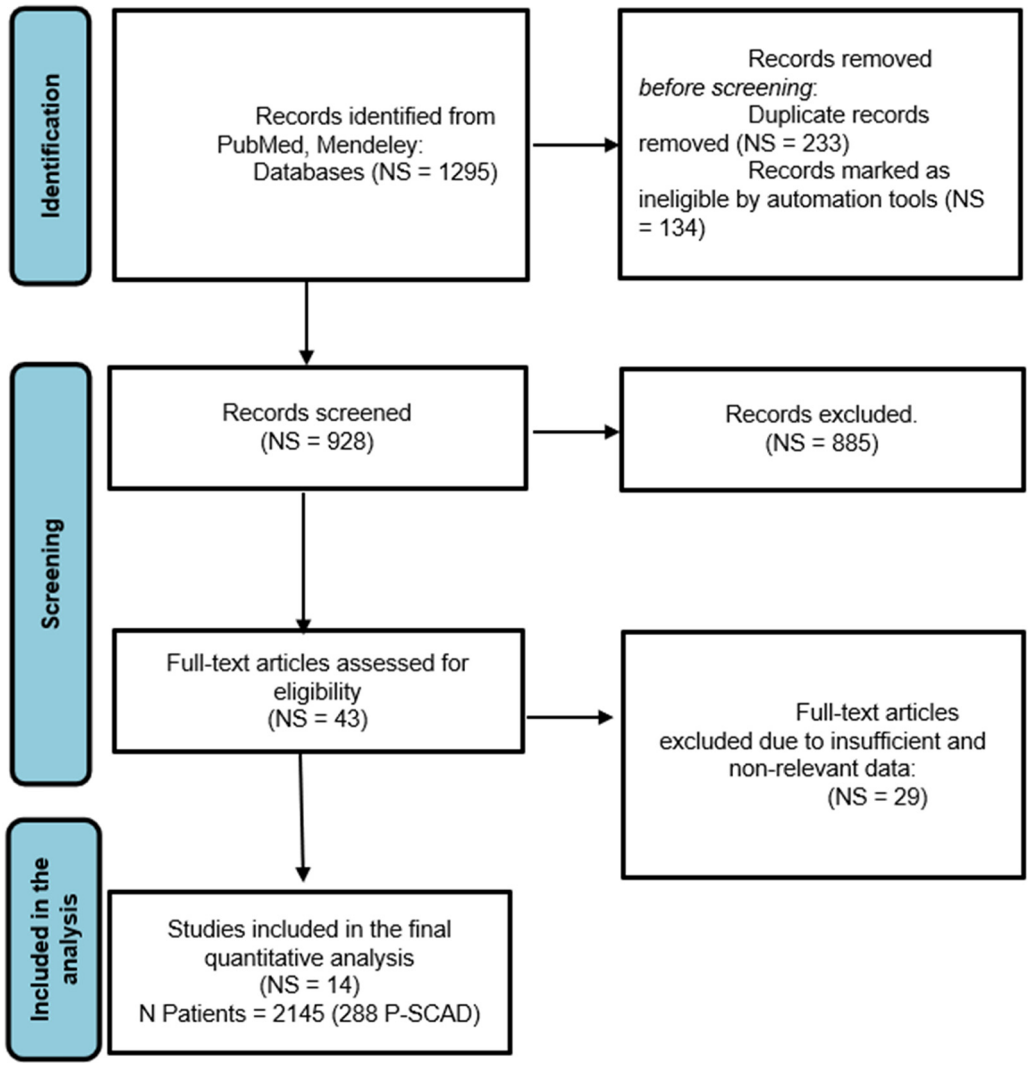


FIGURE 1
PRISMA flow chart of the systematic literature review and article identification process included in the meta-analysis. NS, number of analyzed studies with acute myocardial infarction and SCAD; *N*, number of total SCAD female patients; P-SCAD, pregnancy related spontaneous coronary artery disease.

and repeated on 07 June 2023 to ensure up-to-date results. Relevant literature for this review was obtained by combining MeSH terms and keyword searches. These terms were further combined using "OR" or "AND" Boolean operators, and the use of $/* was employed where applicable. For more details on the search strategy, please refer to Appendix 1.

2.4 Data collection process

Data extraction was conducted from the included studies, covering the characteristics of the study population, study design, demographic and clinical characteristics of SCAD, risk factors, clinical presentation, treatment and management, outcomes, coronary territory, and obstetrical history. The extracted data were systematically organized into tables and compared. The study's primary outcomes focused on clinical presentations, treatment and management, coronary territory, and outcomes (deaths, recurrent SCAD) in SCAD females. Missing data were not input into the analysis.

A quality assessment was carried out using the Downs and Black tools. The Downs and Black score, ranging from 0 to 27, was categorized into three tiers: good (≥20), fair (15–19), and poor (≤14).

Subgroup analysis was performed to compare age, presence of STEMI, conservative treatment, CABG, and death and recurrent SCAD between pregnant SCAD and non-pregnant SCAD females. Although we intended to assess BMI and PCI, these outcomes were not reported in studies with P-SCAD. Unfortunately, sensitivity analysis could not be performed due to the limited number of included studies.

2.5 Statistical analysis

The outcomes were treated as a dichotomous variable: presence of risk factors (yes/no), clinical presentations (yes/no), treatment and management (conservative treatment (yes/no), CABG (yes/no), recurrent SCAD (yes/no), with respective 95% confidence interval (95% CI). Statistical heterogeneity was assessed with the I^2 statistic, and significance was assumed when the I^2 was greater than 50%. The I^2 statistic illustrates the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling error. In the first part, we performed a proportional meta-analysis of the prevalence of risk factors, baseline characteristics, clinical presentation of ACS, treatment, SCAD coronary territory and outcomes using Der Simonian–Laird binary random or Peto fixed-effect meta-analysis in Open Meta. Results from the proportional meta-analysis were tabulated and graphically displayed in Table 7. Secondly, we compared risk factors, clinical presentation of ACS, treatment, coronary territory and outcomes between pregnant SCAD and non-pregnant SCAD using Peto fixed-effect meta-analysis in Review Manager Version 5.4.1. A p-value <0.05 was considered significant. Subgroup analyses were graphically presented by forest plot. Publication bias was not estimated following the recommendations for proportional meta-analysis (11).

3 Results

Figure 1 shows the PRISMA flow chart, from search and identification studies to inclusion in the meta-analysis. After removing duplicates, the abstracts of 928 articles were screened. In the screening process, 885 articles were excluded. The full text of the remaining 43 articles was assessed for eligibility. Of these, 29 studies containing male and female patients with SCAD were excluded because risk factors, treatment, and outcome data were not differentiated between men and women. Hence, fourteen (7, 8, 12–17, 18, 19–30) studies were included in the quantitative synthesis, with a population of 2,145 females in the generative period with ACS caused by

TABLE 1 Design of included studies, number of pregnancy-related spontaneous coronary artery dissection (P-SCAD) and nonpregnancy-related SCAD of women in the generative period (NP-SCAD) and quality of the studies.

Authors	Year	Country	Study design	Study population	No of generative period female SCAD patients	P-SCAD	Quality assessment
Nakashima et al. (7)	2016	Netherlands	Cohort study	20,195	45	5	15
Daoulah et al. (40)	2021	United States	Observational study	83	42	12	16
Tweet et al. (8)	2017	United States	Mayo SCAD registry	323	323	88	12
Ito et al. (12)	2011	United States	Case series, retrospective study	23	23	7	13
Vautrin et al. (61)	2020	United States	Cohort study	144	51	0	13
Fahmy et al. (17)	2016	United States	Cohort study	288	263	0	12
Tweet et al. (15)	2014	United States	Retrospective study	189	174	26	16
Cauldwell et al. (19)	2020	England	Multicenter retrospective study	79	2	2	13
Havakuk et al. (18)	2017	United States	Case series, retrospective study	120	120	84	11
Chen et al. (30)	2021	United States	Case series, retrospective study	307	307	0	13
Faden et al. (16)	2016	England	Cohort	79	79	0	15
Tweet et al. (14)	2012	United States	Retrospective study	87	71	13	13
Tweet et al. (62)	2020	United States	Cohort study	636	636	18	18
Toggweiler et al. (13)	2012	Switzerland	Cohort study	12	9	2	9

P-SCAD, pregnant spontaneous coronary artery dissection, quality assessment was carried out using the Downs and Black tools.

10.3389/fcvm.2024.1277604

TABLE 2 Summary of age, risk factors and comorbidities of reviewed patients with spontaneous coronary artery dissection (SCAD) in the included studies.

Authors	Nakashima et al. (7)	Daoulah et al. (40)	Tweet et al. (8)	Ito et al. (12)	Vautrin et al. (61)	Fahmy et al. (17)	Tweet et al. (15)	Cauldwell et al. (19)	Havakuk et al. (18)	Chen et al. (30)	Faden et al. (16)	Tweet et al. (14)	Tweet et al. (62)	Toggweiler et al. (13)
Age ± SD, years	41 ± 7	39 ± 13	41 ± 38	45 ± 11	39 ± 5	52 ± 9	44 ± 9	30 ± 6	34 ± 4	44 ± 8	33 ± 5	42 ± 9	38 ± 4	47 ± 9
BMI ± SD, kg/m^2	22.5 ± 4.6	29.0 ± 5.4	25.5 ± 5.0	NA	NA	NA	NA	NA	NA	NA	NA	26.2 ± 5.7	25.0 ± 6.0	NA
Hypertension, *n*	10	7	86	13	9	87	NA	NA	5/95[a]	99	NA	13	6	NA
Smoking, *n*	18	6	86	7	36	32	NA	NA	12/96[a]	NA	NA	NA	4	NA
Dyslipidemia, *n*	6	12	113	5	16	53	NA	NA	9/94[a]	81	NA	7	4	NA
Diabetes mellitus, *n*	NA	6	3	1	4	8	NA	NA	4/95[a]	24	NA	2	1	NA
FMD, *n*	NA	NA	161	NA	NA	191	NA	NA	NA	NA	NA	10	6	NA
Emotional stress, *n*	NA	26	43	4	NA	144	NA	NA	NA	NA	NA	NA	9	NA
Migraines, *n*	NA	17	47	NA	NA	NA	NA	NA	NA	NA	NA	NA	9	NA
Thyreoidism, *n*	NA	NA	51	NA	NA	NA	NA	NA	NA	NA	NA	NA	2	NA
IVF, *n*	NA	NA	15	NA	NA	NA	NA	NA	NA	6	NA	1	3	NA
Hormonal therapy, *n*	1	5	59	NA	NA	NA	NA	NA	7/38 (?)	18	NA	11	NA	NA
Contraception, *n*	0	NA	NA	2	NA	NA	NA	NA	NA	NA	NA	5	NA	NA
Eclampsia, *n*	NA	NA	1	NA	NA	NA	NA	NA	8/65 (?)	NA	NA	NA	NA	NA

NA, not available—unavailability of data for the examined group of female patients in the generative period; BMI, body mass index; FMD, fibromuscular dysplasia; IVF, *in vitro* fertilization.
[a]Data were not provided for all the patients.

TABLE 3 Clinical presentations of ACS overall in pregnancy-related spontaneous coronary artery dissection (P-SCAD) and nonpregnancy-related SCAD of women in the generative period (NP-SCAD) in the reviewed studies (summary of acute coronary syndrome SCAD).

Authors	Unstable angina	Cardiac arrest	STEMI	NSTEMI
Nakashima et al. (7)	NA	1/45	39/45	NA
Daoulah et al. (40)	24/42	NA	24/42	18/42
Tweet et al. (8)	8/323	33/323	128/323	186/323
Ito et al. (12)	11/23	1/23	11/23	11/23
Vautrin et al. (61)	NA	1/51	51/51	0/51
Fahmy et al. (17)	NA	NA	73/263	190/263
Tweet et al. (15)	NA	NA	NA	NA
Cauldwell et al. (19)	NA	NA	NA	NA
Havakuk et al. (18)	28/120	NA	87/120	28/120
Chen et al. (30)	NA	NA	89/370	NA
Faden et al. (16)	NA	9/79	42/79	24/79
Tweet et al. (14)	5/71	NA	32/71	34/71
Tweet et al. (62)	1/636	NA	8/636	14/636
Toggweiler et al. (13)	NA	NA	6/9	3/9

NA, not available, unavailability of data for the examined group of female patients in the generative period; ACS, acute coronary syndrome; SCAD, spontaneous coronary artery dissection; P-SCAD, pregnancy-related SCAD; NP-SCAD, non-pregnancy related SCAD; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction.

SCAD (257 pregnancy—associated with SCAD—12.0% of patients) (Table 1). The general timeline of these studies ranged from 2011 to 2021. The median age of the female (in the generative period) SCAD population was approximately 41 years (33–52 years).

Analyzed characteristics of included studies: baseline clinical characteristics, clinical presentations ACS, risk factors, treatment, SCAD coronary territory, and outcomes are presented in Tables 1–6. The quality of the studies was generally poor and fair, ranging from 9 to 18 (median 13, average 13.5). Of the 14 studies examined, five were fair quality, scoring 15–18, and nine were poor quality, scoring 9–13 on the modified Downs and Black scale. Meta-analysis was conducted on baseline characteristics, clinical presentation of ACS, treatment, SCAD coronary territory, and in-hospital outcomes (Table 7). The most common risk factors were smoking history 24.9% (95% CI: 13–36.8) and hypertension 22.1% (95% CI: 11.3–32.9). There is not enough data to make a difference in the prevalence of smoking history and hypertension between pregnant and non-pregnant patients. There are no data on whether a new-onset increment of blood pressure was the reason for the occurrence of SCAD or whether the patient was treated for hypertension before. Occurrences of dyslipidemia and diabetes mellitus in analyzed female patients in the generative period with SCAD were 19.4% (95% CI: 9–29.7) and 3.3% (95% CI: 1.5–5.1). The most common clinical presentations of acute coronary syndrome were STEMI in 47.4% (95% CI: 28.5–66.2) and NSTEMI in 39.8% (95% CI: 15.2–64.4) of cases. Conservative treatment was used in 41.1% of patients (95% CI: 23.2–59.1). The percutaneous coronary intervention (PCI) was performed in 32.7% (95% CI: 19.9–

TABLE 4 Aggregate initial treatment of pregnancy-related spontaneous coronary artery dissection (P-SCAD) and nonpregnancy-related SCAD of women in the generative period (NP-SCAD) cases in the reviewed studies (summary of treatment of reviewed studies).

Authors	Nakashima et al. (7)	Daoulah et al. (40)	Tweet et al. (8)	Ito et al. (12)	Vautrin et al. (61)	Fahmy et al. (17)	Tweet et al. (15)	Cauldwell et al. (19)	Havakuk et al. (18)	Chen et al. (30)	Faden et al. (16)	Tweet et al. (14)	Tweet et al. (62)	Toggweiler et al. (13)
Number of female SCAD patients	45	42	323	23	51	263	174	2	120	307	79	71	636	9
Conservative treatment	27	21	NA	14	0	225	87	1	54	89	8	37	13	NA
Stent	NA	21	NA	4	22	38	82	1	37	68	31	43	9	NA
CABG	NA	2	NA	4	2	0	NA	NA	27	3	26	7	2	NA
BB	NA	38	NA	NA	40	NA	NA	2	NA	NA	NA	NA	NA	NA
ACEI	NA	23	NA	NA	14	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ca ant	NA	3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Aminoacyl acid therapy	NA	4	NA	NA	50	NA	NA	2	NA	NA	NA	NA	NA	NA
Purinergic receptor P2Y, G-protein coupled, 12 protein therapy	NA	42	NA	NA	47	NA	NA	2	NA	NA	NA	NA	NA	NA
Anticoagulant therapy	NA	NA	NA	NA	38	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA, not available—unavailability of data for the examined group of female patients in the generative period; SCAD, spontaneous coronary artery dissection; CABG, coronary artery bypass graft surgery; BB, beta blockers; ACEI, angiotensin-converting enzyme inhibitors; Ca ant, Calcium antagonist.

TABLE 5 Vessel involvement overall in pregnancy-related spontaneous coronary artery dissection (P-SCAD) and nonpregnancy-related SCAD of women in the generative period (NP-SCAD) in the reviewed studies (summary of SCAD coronary territory were involvement of reviewed studies).

Authors	Nakashima et al. (7)	Daoulah et al. (40)	Tweet et al. (8)	Ito et al. (12)	Vautrin et al. (61)	Fahmy et al. (17)	Tweet et al. (15)	Cauldwell et al. (19)	Havakuk et al. (18)	Chen et al. (30)	Faden et al. (16)	Tweet et al. (14)	Tweet et al. (62)	Toggweiler et al. (13)
Number of female SCAD patients	45	42	323	23	51	263	174	2	120	307	79	71	636	9
LAD, *n*	NA	17	199	16	28	NA	NA	1	NA	168	NA	51	13	NA
LCX, *n*	4	5	47	6	4	NA	25	NA	28	108	NA	13	4	NA
LM, *n*	0	8	26	1	0	NA	4	NA	43	7	NA	8	2	NA
RCA, *n*	15	9	46	5	12	NA	25	NA	18	69	NA	21	4	NA
Multivessel, *n*	7	2	57	6	7	NA	15	NA	48	34	NA	18	6	NA

NA, not available—unavailability of data for the examined group of female patients in the generative period. SCAD, spontaneous coronary artery dissection; LAD, left anterior descending artery; LCX, circumflex artery; LM, left main coronary artery; RCA, right coronary artery.

10.3389/fcvm.2024.1277604

10.3389/fcvm.2024.1277604

TABLE 6 Findings of early outcomes of patients with spontaneous coronary artery dissection—overall in pregnancy-related spontaneous coronary artery dissection (P-SCAD) and nonpregnancy-related SCAD of women in the generative period (NP-SCAD) in the reviewed studies (summary of outcomes of reviewed studies (intrahospital/short outcome).

Authors	Nakashima et al. (7)	Daoulah et al. (40)	Tweet et al. (8)	Ito et al. (12)	Vautrin et al. (61)	Fahmy et al. (17)	Tweet et al. (15)	Cauldwell et al. (19)	Havakuk et al. (18)	Chen et al. (30)	Faden et al. (16)	Tweet et al. (14)	Tweet et al. (62)	Toggweiler et al. (13)
Number of female SCAD patients	45	42	323	23	51	263	174	2	120	307	79	71	636	9
Composite endpoint, *n*	17	NA	NA	NA	NA	NA	NA	6	NA	85	NA	NA	NA	NA
Reduced EF, *n*	NA	NA	16	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Death, n	1	NA	0	0	1	51	NA	3	5	1	3	NA	NA	NA
Non-fatal MI, *n*	16	NA	NA	2	8	NA	NA	1	NA	NA	66	NA	NA	NA
Recurrent SCAD, *n*	12	NA	33	1	NA	NA	NA	2	NA	36	NA	15	NA	2
Progression of residual SCAD, *n*	12	NA	NA	1	NA	NA	NA	NA	NA	44	NA	NA	NA	NA
Urgent revascularization, *n*	0	NA	20	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA, not available—unavailability of data for the examined group of female patients in the generative period; SCAD, spontaneous coronary artery dissection; EF, ejection fraction; MI, myocardial infraction.

45.4), and coronary artery bypass grafting (CABG) was done in 3.8% (95% CI: 0.2–5.7) of patients. The most affected artery was LAD in 50.5% (95% CI: 21.9–79.1). Multivessel SCAD was diagnosed in 15.5% (95% CI: 8.6–22.3) of patients. In the analysis of the clinical outcomes, including mortality, non-fatal MI and recurrent SCAD, the prevalence of mortality was 3.3% (95% CI: 1.4–5.1), while non-fatal MI and recurrent SCAD had 37.7% (95% CI: 1.9–73.4) and 15.2% (95% CI: 9.1–21.3) of included patients (Table 7).

The analysis of pooled data showed a significant difference in age between P-SCAD and NP-SCAD patients (mean difference was 14.3 years, $p < 0.001$, $I^2 = 0\%$), (Figure 2). The prevalence of STEMI was evaluated in 4 out of 14 studies. The meta-analysis result indicated that the prevalence of STEMI was significantly more frequent in patients with P-SCAD compared to those with NP-SCAD (OR = 3.16; 95% CI: 2.30–4.34; $I^2 = 64\%$) (Figure 3). The prevalence of affected left main was evaluated in 3 out of 14 studies. The meta-analysis result indicated that the prevalence of left main involvement was significantly more frequent in P-SCAD compared to women with NP-SCAD (OR = 14.34; 95% CI: 7.71–26.67; $I^2 = 54\%$) (Figure 4). The prevalence of LAD involvement was evaluated in 3 out of 14 studies. The meta-analysis result indicated that the LAD was more frequently affected in women with P-SCAD compared to those with NP-SCAD (OR = 1.57; 95% CI: 1.06–2.32; $I^2 = 23\%$) (Figure 4). The prevalence of conservative management was evaluated in 3 of 14 studies. The meta-analysis result indicated that the prevalence of conservative management was significantly higher in NP-SCAD vs. P-SCAD patients (OR = 0.61; 95% CI: 0.37–0.98; $I^2 = 0\%$) (Figure 5). The prevalence of CABG was evaluated in 3 of 14 studies. The meta-analysis result indicated that the higher prevalence of CABG was reported in P-SCAD patients compared to another group (OR = 6.29; 95% CI: 4.08–9.70; $I^2 = 0\%$) (Figure 5). The prevalence of recurrent SCAD was evaluated in 3 of 14 studies. The meta-analysis result indicated that the prevalence of recurrent SCAD was not significantly higher in patients with P-SCAD compared to NP-SCAD cases (OR = 2.54; 95% CI: 0.97–6.61; $I^2 = 0\%$) (Figure 6). Mortality was evaluated in 3 of 14 studies. The meta-analysis result indicated that the mortality was not significantly higher in women with P-SCAD vs. NP-SCAD cases (OR = 1.13; 95% CI: 0.06–21.16; I^2 = not applicable) (Figure 7).

4 Discussion

SCAD is an increasingly recognized presentation of AMI, especially in young women (20). A particularly vulnerable population of patients is represented by pregnant women and the period after childbirth, where the onset of myocardial infarction caused by SCAD poses a danger for both the mother and the child, with great uncertainty if another pregnancy is planned. Mortality from infarction caused by SCAD is not negligible, especially since no data from randomized studies would show us guidelines for treating such patients (21).

10.3389/fcvm.2024.1277604

TABLE 7 Meta-analysis of the prevalence of risk factors, treatment, involvement in coronary territory and early outcomes—pooled studies.

	No. of studies	Total cases	Prevalence [95% CI]		I^2 (%)	*p*-value
Baseline characteristics						
Hypertension	10	335	22.1 [11.3–32.9]		97.8	<0.001
Diabetes mellitus	9	53	3.3 [1.5–5.1]		83.8	<0.001
Dyslipidemia	10	306	19.4 [9–29.7]		97.6	<0.001
Smoking	8	201	24.9 [13–36.8]		97.7	<0.001
					95.9	
Clinical presentation						
Unstable angina	6	77	14.6 [8.6–20.7]			<0.001
Cardiac arrest	5	45	5.9 [1.6–10.2]		74.9	0.003
STEMI	11	539	47.4 [28.5–66.2]		99.1	<0.001
NSTEMI	9	508	39.8 [15.2–64.4]		99.3	<0.001
					99.4	
Treatment and management						
Conservative	12	579	41.1 [23.2–59.1]			<0.001
Stent	11	356	32.7 [19.9–45.4]		97.9	<0.001
CABG	9	73	3.8 [0.2–5.7]		90.9	<0.001
					99.3	
Coronary territory						
LAD involvement	8	493	50.5 [21.9–79.1]			<0.001
Lcx involvement	10	244	15.8 [7.2–24.4]		96.9	<0.001
Left main involvement	10	99	5.9 [3.1–8.8]		92.1	<0.001
RCA involvement	10	224	18.9 [10.7–27.2]		96.3	<0.001
Multivessel	10	200	15.5 [8.6–22.3]		95.6	<0.001
Outcomes						
Death	8	62	3.3 [1.4–5.1]		90.1	<0.001
Non-fatal IM	5	93	37.7 [1.9–73.4]		97.5	<0.001
Recurrent SCAD	7	101	15.2 [9.1–21.3]		75.3	<0.001

SCAD, spontaneous coronary artery dissection; CABG, coronary artery bypass graft surgery; LAD, left anterior descending artery; LCX, circumflex artery; LM, left main coronary artery; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; IM, myocardial infarction

What do we know about SCAD in females in the generative period, especially the risk factors, the natural course of the disease and therapeutic options?

This meta-analysis analyzed 2,145 women with ACS SCAD in the reproductive period; from that number, 257 (12%) had P-SCAD. Most included studies reported overall risk factors in

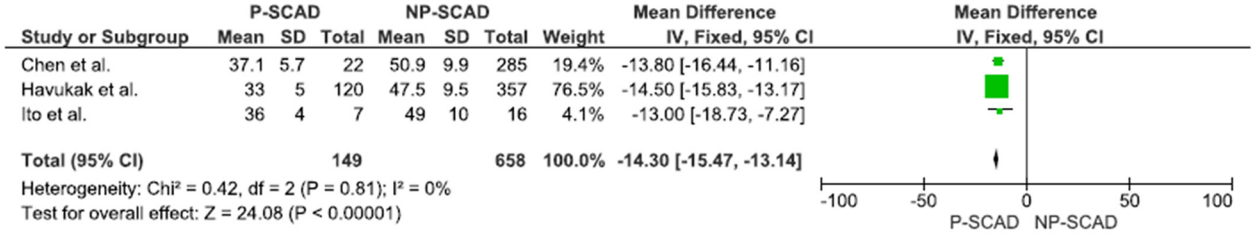


FIGURE 2
Forest plot age difference in pregnant and non-pregnant SCAD females.

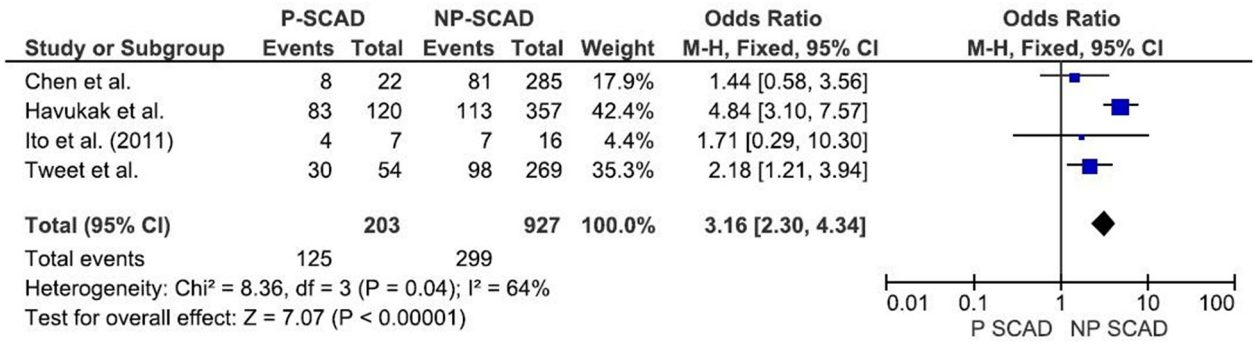


FIGURE 3
Forest plot for STEMI in pregnant and non-pregnant SCAD females.

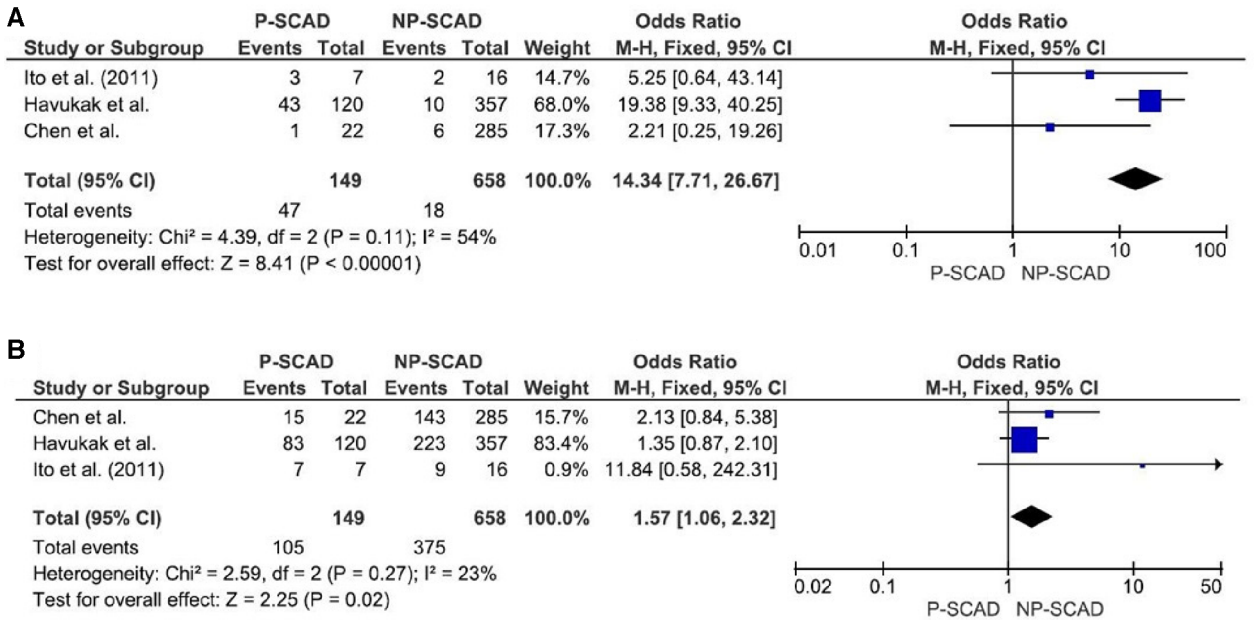


FIGURE 4
Forest plot for LM (A) and LAD (B) in pregnant and non-pregnant SCAD females.

P-SCAD and or overall, for male and female patients with diagnosed SCAD. The limited available information precludes reaching definite conclusions regarding the risk factors for P-SCAD vs. NP-SCAD in the generative period. Only the analysis of the age of females in the generative period, clinical presentation of ACS, SCAD coronary territory, treatment and SCAD recurrence was sufficiently powered to detect differences between P-SCAD vs. NP-SCAD.

4.1 Risk factors and associated pathologies

Statistical data processing showed that smoking history is the most common risk factor 24.9% (95% CI: 13–36.8). There is insufficient data to differentiate the prevalence of smoking history between pregnant and non-pregnant patients, although some studies reported that female smokers have a 2-fold increased risk of myocardial infarction (22, 23). Female smokers taking oral contraceptives are reported to have a 7–100 fold increased risk of myocardial infarction (22). The association between smoking can be explained through increased oxidative stress and sympathetic activity, which may predispose patients to an increased risk of acute coronary syndrome (22–24).

We found that the second most common risk factor is hypertension 22.1% (95% CI: 11.3–32.9). There is insufficient data to differentiate the prevalence of hypertension between pregnant and non-pregnant patients. There is no information on

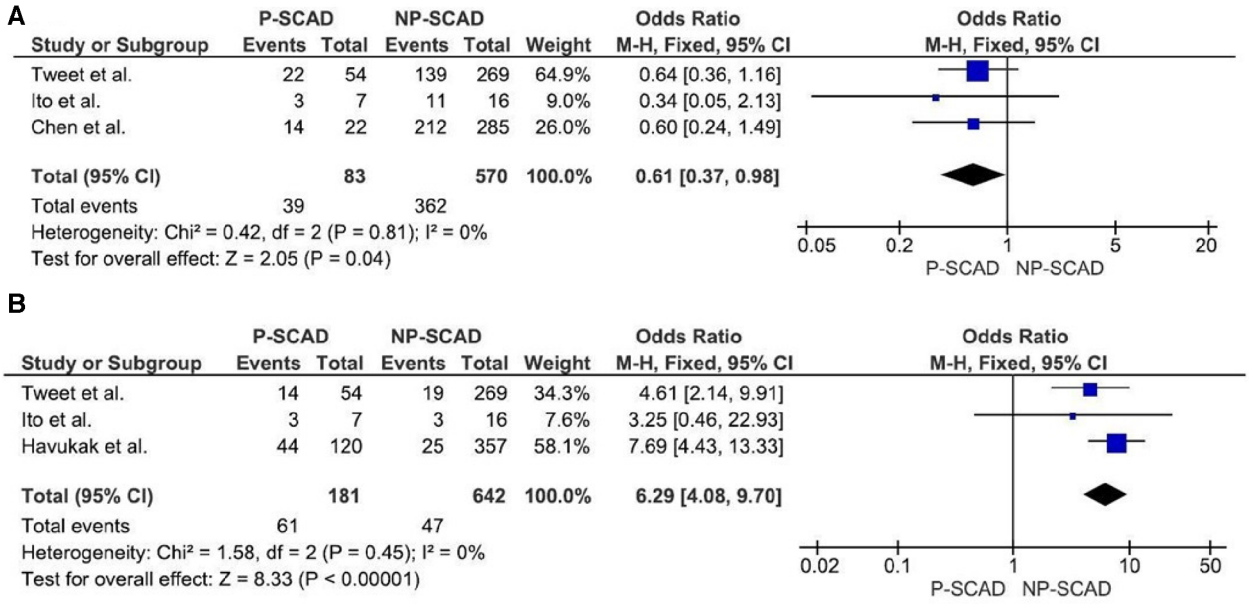


FIGURE 5
Forest plot for conservative management (A) and CABG (B) in pregnant and non-pregnant SCAD females.

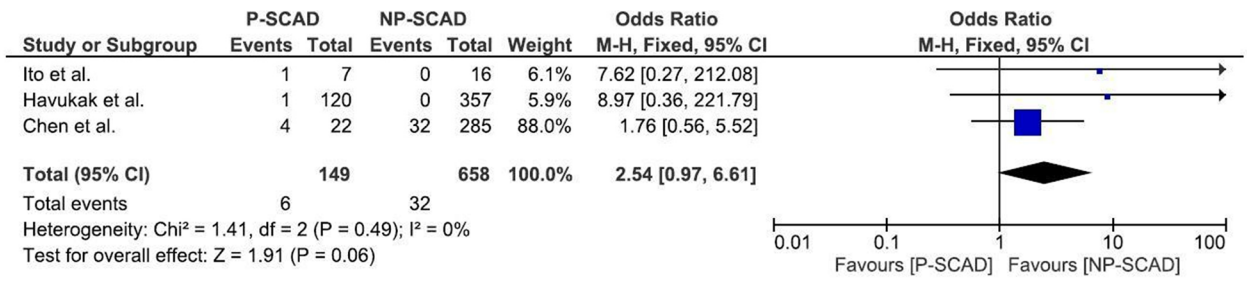


FIGURE 6
Forest plot for recurrent SCAD in pregnant and non-pregnant SCAD females.

whether the sudden rise in blood pressure was the reason for the appearance of SCAD or whether the patient had a previous history of treated hypertension (25).

The pooled data of prevalence of dyslipidemia and diabetes mellitus among analyzed female patients in the generative period were 19.4% (95% CI: 9–29.7) and 3.3% (95% CI: 1.5–5.1). Data that support the hypothesis about the association between dyslipidemia and diabetes mellitus and their role in causing SCAD is that adipose tissue is also an endocrine organ that produces hormones, peptides and nonpeptides that affect cardiovascular homeostasis. Adipose tissue is a significant source of estrogens, angiotensinogen and markers of chronic inflammation that can trigger acute coronary syndrome: tumor necrosis factor alpha, interleukin-6 and plasminogen activator inhibitor-1 (26).

SCAD is often associated with "few or no traditional cardiovascular risk factors" (14). SCAD patients have a lower prevalence of traditional cardiovascular risk factors than the national, age-matched average. It is known that some risk factors such as hypertension are similar with age matched national prevalence. Therefore, SCAD should be considered in the differential diagnosis of young men and women who present with ACS even in the presence of traditional risk factors (27). Patients with ACS caused by SCAD found to have high prevalence of hypothyroidism that those with atherosclerotic ACS (28). Freire et al. showed that hypothyroidism was more associated with diffuse and distal coronary lesions with SCAD, which were mostly managed conservatively (29). Also hypothyroidism has been associated with a higher frequency of iatrogenic coronary artery dissection during angioplasty (28). Although Faden et al. did not connect hypothyroidism with increased risk for SCAD (16).

The incidence of traditional risk factors for coronary artery disease (CAD) is lower or similar in pregnant patients with SCAD compared to those with atherosclerotic myocardial infarction at similar age (8, 12, 18, 23, 30). Zeven et al. found

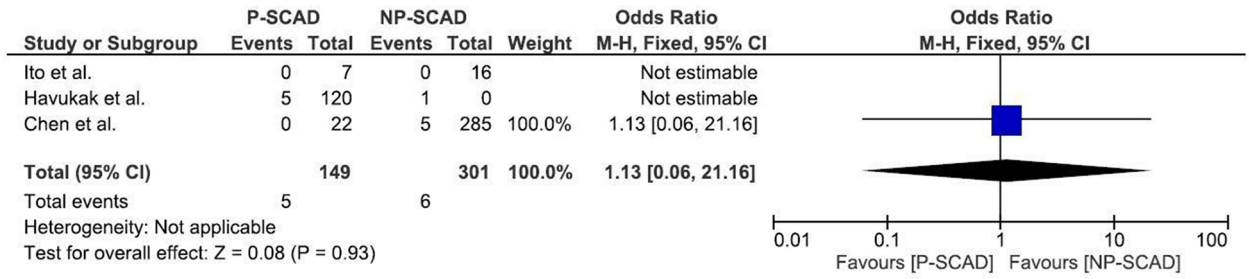


FIGURE 7
Forest plot for mortality in pregnant and non-pregnant SCAD females.

that patients at a third trimester have a highest risk for SCAD. In other studies the highest incidence of SCAD was reported in so called peripartum (which includes delivery and 1 week after delivery) and postpartum period up to 30 days after giving birth (2). The most frequent contributing factors for P-SCAD include genetics, hormonal influences, systemic inflammatory diseases, inherited or acquired arteriopathies, and environmental factors. Special attention is given to high levels of estrogen in P-SCAD which influences the arterial wall structure. Estrogen leads to increased activity of metalloproteases which can lead to weakening od arterial wall and its dissection. In accordance with the previous, the hormonal exposure during *in vitro* fertilization (IVF) is associated with an increased risk for vascular dissection in treated women during and after the IVF process (31, 32). Further, hormonal therapy was found to be a potential cause of SCAD in non-pregnant women (7, 18). We did not find publications where direct and significant correlation between the use of oral contraceptives and SCAD was determined.

4.2 Precipitating stressors

Some studies mark emotional stress as a trigger for SCAD because it correlates with catecholamines (7, 16, 33–37). It is believed that catecholamines may cause structural changes in the arterial wall leading to intimal rupture or disruption of the vasa vasorum, possibly through increased myocardial contractility or vasospasm (7). Some studies emphasize the association between migraine and arterial dissection, which is explained by the hypothesis of extracellular matrix defect (16, 38). Patients with migraine could be predisposed to vascular injury and endothelial dysfunction possibly due to genetic factors or hormones (39). The sample size and available data of precipitating stressors between the P-SCAD and NP-SCAD groups were too small to confirm the statistical contribution of all precipitating stressors to diagnosed SCAD.

4.3 Coronary territory

The main mechanism of myocardial injury in SCAD is ischemia induced by coronary artery narrowing of varying degrees due to intramural hematoma formation after intimal disruption (40). The main difference in the pathophysiology of different types of SCAD is the precipitating factors and causes that lead to arterial wall weakening (40). The meta-analysis result indicated that the prevalence of left main (LM) was significantly associated with P-SCAD (OR = 14.34; 95% CI: 7.71–26.67; $I^2 = 54\%$). These findings are consistent with previous reports of LM involvement, including preliminary results of the Dissection of Coronary Arteries: Veneto and Emilia Registry (DISCOVERY) study (41).

The meta-analysis result indicated that the prevalence of LAD involvement is significantly more prevalent in P-SCAD group (OR = 1.57; 95% CI: 1.06–2.32; $I^2 = 23\%$). Compared with non-pregnant women with SCAD, P-SCAD is associated with more extensive involvement of the coronary arteries manifested by a significantly higher rate of LM and multivessel dissections (12, 18). SCAD in postpartum involved more proximal coronary segments and LAD, which likely led to higher peak troponin I level, lower left ventricular ejection fraction, and more frequent congestive heart failure on presentation (12). In addition, there is a markedly higher incidence of STEMI and involvement of the left ventricle (LV) anterior wall, and as a result, a marked decrease in LV ejection fraction compared with non-pregnant patients. There is an increased incidence of cardiogenic shock, life-threatening arrhythmias, a need for emergent CABG surgery, use of mechanical support and cardiac transplantation, and a higher rate of maternal and fetal mortality in patients with SCAD in peripartum period. Percutaneous coronary interventions (PCI) are associated with a low success rate and high incidence of complications, including iatrogenic dissections and propagation of existing dissections requiring emergency CABG surgery, in the same group of patients (18).

4.4 Therapeutic strategies

P-SCAD is potentially the most devastating variant of SCAD. Currently, the scientific community works with limited information about P-SCAD, and a major dilemma is the optimal treatment. While some of the authors suggest that conservative

treatment is by far superior to percutaneous intervention (42), there are some scenarios where invasive treatment may be a better option for acute management of P-SCAD (2, 43). The rarity of this entity and the lack of randomized studies, and the complications of invasive treatment make it challenging to choose between conservative management, PCI or CABG (44). The optimal management of SCAD is still unknown. All recommendations are provided by experts' opinions on treating individual cases of SCAD. Conservative management was usually carried out in hemodynamically stable patients without ongoing ischemia or complex angiographic findings- involving the left main coronary artery (45).

Conservative treatment was used in 41.1% (95% CI: 23.2–59.1) of cases. The meta-analysis result indicated that the NP-SCAD patients significantly more frequently received conservative treatment than P-SCAD group (OR = 0.61; 95% CI: 0.37–0.98; $I^2 = 0\%$) (Figure 5). In the NP-SCAD group, 362 (63.5%) out of 570 women with SCAD underwent conservative treatment. This meta-analysis showed that a non-invasive approach to SCAD treatment is favored for hemodynamically stable patients with NP-SCAD, which confirms the results of previous studies. Although heparin is indicated in patients with ACS, it is recommended to discontinue the anticoagulation therapy after angiographic findings of SCAD to minimize bleeding and enable intramural hematoma to organize (46).

According to the contemporary guidelines, in SCAD patients undergoing subsequent PCI, dual antiplatelet therapy (DAPT) is recommended. The duration of dual antiplatelet therapy after PCI is recommended during 12 months if patients are not on high bleeding risk (46). The optimal duration of monotherapy after 12 months in SCAD patients after PCI remains still unknown (46, 47). The use of dual antiplatelet therapy for 12 months, in SCAD patients, was advocated after the publication of studies where in addition to hematoma, an intraluminal thrombus was frequently found on OCT (47). Since the precise mechanisms of the thienopyridine derivatives elimination route is unknown, the use of clopidogrel is not recommended during breastfeeding (48, 49). Also, prescription of thienopyridine derivatives should be done carefully in premenopausal women due to high risk of menorrhagia (2, 50). As well established, use of low-dose acetylsalicylic acid (<150 mg) in the second and third trimesters is safe (48, 51). There are no randomized studies investigating the use of glycoprotein IIb/IIIa inhibitors for SCAD treatment. In only one study it was noted that the use of glycoprotein IIb/IIIa inhibitors is safe in these patients (52). Therefore, the use of DAPT (but not clopidogrel in breastfeeding women) is recommended in P-SACD and NP- SCAD patients after PCI for 12 months. Single antiplatelet therapy (SAPT) or DAPT, and duration of that therapy, in SCAD patients treated conservatively should be individually tailored comparing the ischemic and bleeding risk. In the DISCO register involving women in high percentage (88.9% overall, and 39.5% of them being post-menopausal), investigators compared the prognosis in patients treated with DAPT vs. SAPT during 12 months in conservatively treated patients with SCAD. In those treated with DAPT compared to those treated with SAPT there was a significantly higher incidence of MACE (all-cause death, non-fatal MI, and any unplanned PCI) (53).

Despite their early usage for SCAD treatment, thrombolytic agents are not recommended because of the risk of dissection expansion and worsening of coronary spasm leading to coronary rupture (2, 54).

Beta-blockers significantly reduce the risk of SCAD recurrence, which can be explained by their role in the reduction of arterial wall stress (54). Nitrates, calcium-channel blockers and ranolazine should be prescribed to relieve chest pain (2, 55). Nitrates are also optimal medication for heart failure, concomitant vasospasm, and residual coronary stenosis (54). Optional agents for left ventricular dysfunction are angiotensin-converting enzyme inhibitors, beta-blockers and mineralocorticoid receptor antagonists (MRA) (47). ACE inhibitors should be carefully prescribed because they are contraindicated in pregnancy and the first month of breastfeeding (32). Statins should be prescribed only for preexisting dyslipidemia because the mechanism of atherosclerosis is not usually associated with SCAD. One small study reported higher statin use in patients with SCAD recurrence (14).

Our results have shown that 60% of females included in this study with P-SCAD are initially presented with STEMI, with high rates of LM and LAD involvement. Of the total number of patients, 41.1% were conservatively treated (95% CI: 23.2–59.1), 32.7% underwent PCI intervention (95% CI: 19.9–45.4), and 3.8% were treated with CABG (95% CI: 0.2–5.7).

In P-SCAD patients, more invasive treatments are performed, typically involving PCI and CABG, vs. a purely conservative approach which was found to be less effective for P-SCAD patients (47). According to the meta-analysis results, the CABG surgery was significantly more frequent in P-SCAD compared to NP-SCAD patients (OR = 6.29; 95% CI: 4.08–9.70; $I^2 = 0\%$). Included studies have not supplied enough data to perform a meta-analysis about PCI interventions. Factors favoring CABG vs. other therapeutic options are hemodynamic instability, failed PCI, complex coronary anatomy, three-vessel disease, LM involvement, deterioration after the initial conservative approach and ongoing ischemia and SCAD extension in the first 48 h (56).

In the study of Havakuk et al., most of the patients were presented during the postpartum period or the third trimester and none during the first trimester (18). They suggested that timing of presentation should be helpful in predicting SCAD in women with pregnancy-associated myocardial infarction. CABG surgery was done immediately after emergent CS in 6 cases and during pregnancy in 4 women. Fetal mortality was reported in 3 of the cases, all of them in women with LM dissection. Two were related to CABG surgery. Maternal mortality occurred in 5 patients. None of the described cases had a history of conventional cardiovascular disease risk factors, although one woman was diagnosed with Ehler–Danlos syndrome. Four cases presented postpartum and 1 antepartum (18).

The choice between revascularization and conservative therapy for SCAD depends on various factors, including the severity and location of the dissection, the presence of ongoing symptoms, and the patient's

hemodynamic conditions. There is ongoing debate and limited evidence regarding the optimal approach, as randomized controlled trials specific to SCAD are scarce (2, 21, 42, 57).

Alfonso et al., in their prospective study of 45 patients, suggested as first-choice a "watchful waiting" approach in stable patients, with a possible switch to revascularization in case of ongoing or recurrent ischemia (51). PCI is accompanied by a risk of adverse events, including an extension of the dissection, guidewire passage into the false lumen and major side branch restriction or occlusion by the propagation of hematoma (47).

It is important to recognize that while P-SCAD is concerning, the prognosis and outcomes can vary widely among individuals. Early recognition, prompt medical intervention, and ongoing support and follow-up care can help manage the condition effectively.

In the most recent retrospective cohort study, Felbaum et al. showed that trends in therapeutic options drastically changed over time (58). In this center, the proportion of patients undergoing revascularization with CABG significantly decreased over a period: 23% of patients were revascularized with CABG before 2013, whereas no patients underwent CABG in 2018–2019. Authors concluded that patients undergoing revascularization with PCI or CABG were more likely to be younger and have pregnancy-associated SCAD, dissection of the left main or left anterior descending artery, and multivessel involvement. This supports the premise that spontaneous arterial healing with conservative management after SCAD is linked to good clinical outcomes (55, 58).

4.5 Outcomes

4.5.1 Recurrence rate

The recurrence rate of SCAD in pregnant women has been reported to range from 10% to 29% in various studies (59). Most recurrences tend to happen within the first year after the initial SCAD event, with a peak incidence in the first 4 to 6 months (21). The prevalence of recurrent SCAD was evaluated in 3 of 14 studies. Of 149 pregnant women with spontaneous coronary artery dissection, 6 had recurrent SCAD. In 32 women out of 658 in the reproductive period who were not pregnant, recurrent SCAD was reported. Our meta-analysis result indicated that the prevalence of recurrent SCAD was not significantly more frequent in P-SCAD than in NP-SCAD group, as previously reported.

It is important to note that these rates may not be universally applicable, and individual cases may vary. Due to the limited data on mortality and recurrence rates, specifically in pregnant women with SCAD, medical professionals must provide tailored care and closely monitor patients who experience this condition during pregnancy. Recurrent ischemic events because of persistent or new spontaneous coronary artery dissection are common during long-term follow-up (18, 40).

4.5.2 Mortality rate

Notably, SCAD mortality rates in women are generally lower than those observed in men with traditional atherosclerotic coronary artery disease. However, the risk of mortality in SCAD can still be significant, including the severity and extent of the dissection, underlying risk factors or comorbidities, and the timeliness and effectiveness of medical intervention. Several studies have reported mortality rates ranging from 0% to around 10%, with higher rates in specific subgroups (14).

The mortality and recurrence rates of SCAD in pregnant women are areas of ongoing research, and limited specific data is available. However, several studies have provided insights into these aspects of SCAD in pregnant women. In a retrospective study conducted by Tweet et al., which included 12 pregnant women with SCAD, the overall mortality rate was reported to be 8.3% (60). In a larger retrospective study by Saw et al., which included 87 women with SCAD, 6.9% of the cases occurred during pregnancy (1). The mortality rate in the pregnant group was reported to be 5.3% (33).

Of note, mortality rates may vary among different studies due to differences in patient populations and methodologies. In our analysis of the clinical outcomes, including mortality and non-fatal myocardial infarction (MI) and recurrent SCAD, the prevalence of mortality was 3.3% (95% CI: 1.4–5.1), while estimated prevalence of non-fatal MI and recurrent SCAD was 37.7% (95% CI: 1.9–73.4) and 15.2% (95% CI: 9.1–21.3) (Table 1).

Mortality was evaluated in 3 of 14 studies. Of 149 pregnant women with SCAD, death was the outcome in 6 women, while out of 658 women in the generative period who were not pregnant, 32 died. The meta-analysis result indicated that mortality is not significantly higher in P-SCAD compared to NP-SCAD patients as reported by some studies (18) (Figure 7).

4.6 Limitations

This study has several limitations and strengths. Firstly, it was limited to publications available in the English language and was focused on observational studies. Secondly, there was substantial variation in sample sizes across the included studies. Thirdly, high heterogeneity and a limited number of studies prevented a full meta-regression and subgroup meta-analysis; therefore, all findings must be interpreted cautiously. In the proportional meta-analysis, we used random effect due to the heterogeneity of included studies. Unfortunately, sensitivity analysis could not be performed due to the limited number of studies.

5 Conclusion

There is great heterogeneity in the methodology of examining the risk for the occurrence of SCAD as well as the decisions for the therapeutic approach in females in the generative period.

Female patients with P-SCAD have more frequently STEMI with involved left main and LAD compared to NP-SCAD patients. Women with NP-SCAD are treated conservatively in higer percentage than P-SCAD patients. Interstingly, P-SCAD compared to NP-SCAD patients do not have significantly higher mortality rates or recurrent coronary dissection.

Developing specialized SCAD registries and research efforts has also contributed to a better understanding of the condition and its outcomes.

Author contributions

SA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. AI: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing, Validation. DS: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. DR: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. MN: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. JM: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. TF: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. KK: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. IM: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. AD: Conceptualization, Writing – review & editing. GK: Conceptualization, Writing – review & editing. ZM: Conceptualization, Writing – review & editing. II: Conceptualization, Writing – review & editing. SA: Conceptualization, Writing – review & editing. VP: Conceptualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Saw J, Mancini GJ, Humphries K, Fung A, Boone R, Starovoytov A, et al. Angiographic appearance of spontaneous coronary artery dissection with intramural hematoma proven on intracoronary imaging. *Catheter Cardiovasc Interv*. (2016) 87 (2):E54–61. doi: 10.1002/ccd.26022

2. Zeven K. Pregnancy-associated spontaneous coronary artery dissection (SCAD) in women: a literature review. *Curr Ther Res*. (2023) 98:100697. doi: 10.1016/j.curtheres.2023.100697

3. Maehara A, Mintz GS, Castagna MT, Pichard AD, Satler LF, Waksman R, et al. Intravascular ultrasound assessment of spontaneous coronary artery dissection. *Am J Cardiol*. (2002) 89(4):466–8. doi: 10.1016/S0002-9149(01)02272-X

4. Sheikh AS, O'Sullivan M. Pregnancy-related spontaneous coronary artery dissection: two case reports and a comprehensive review of literature. *Heart Views*. (2012) 13(2):53. doi: 10.4103/1995-705X.99229

5. Yip A, Saw J. Spontaneous coronary artery dissection—a review. *Cardiovasc Diagn Ther*. (2015) 5(1):37. doi: 10.3978/j.issn.2223-3652.2015.01.08

6. Manalo-Estrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol*. (1967) 83(4):336–41. PMID: 4225694

7. Nakashima T, Noguchi T, Haruta S, Yamamoto Y, Oshima S, Nakao K, et al. Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: a report from the angina pectoris–myocardial infarction multicenter investigators in Japan. *Int J Cardiol*. (2016) 207:341–8. doi: 10.1016/j.ijcard.2016.01.188

8. Tweet MS, Hayes SN, Codsi E, Gulati R, Rose CH, Best PJ. Spontaneous coronary artery dissection associated with pregnancy. *J Am Coll Cardiol*. (2017) 70(4):426–35. doi: 10.1016/j.jacc.2017.05.055

9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *International Journal of Surgery*. (2021) 88:105906. doi: 10.1016/j.ijsu.2021.105906

10. Abbara S, Kalva SP. Problem solving in radiology: cardiovascular imaging E-book. *Elsevier Health Sci*. (2012) 848.

11. Barker TH, Migliavaca CB, Stein C, Colpani V, Falavigna M, Aromataris E, et al. Conducting proportional meta-analysis in different types of systematic reviews: a guide for synthesisers of evidence. *BMC Med Res Methodol*. (2021) 21:1–9. doi: 10.1186/s12874-021-01381-z

12. Ito H, Taylor L, Bowman M, Fry E, Hermiller J, Van Tassel J. Presentation and therapy of spontaneous coronary artery dissection and comparisons of postpartum versus nonpostpartum cases. *Am J Cardiol*. (2011) 107(11):1590–6. doi: 10.1016/j.amjcard.2011.01.043

13. Toggweiler S, Puck M, Thalhammer C, Manka R, Wyss M, Bilecen D, et al. Associated vascular lesions in patients with spontaneous coronary artery dissection. *Swiss Med Wkly*. (2012) 142:w13538. doi: 10.4414/smw.2012.13538

14. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. *Circulation*. (2012) 126(5):579–88. doi: 10.1161/CIRCULATIONAHA.112.105718

15. Tweet MS, Eleid MF, Best PJ, Lennon RJ, Lerman A, Rihal CS, et al. Spontaneous coronary artery dissection: revascularization versus conservative therapy. *Circ: Cardiovasc Interventions*. (2014) 7(6):777–86. doi: 10.1161/CIRCINTERVENTIONS.114.001659

16. Faden M, Bottega N, Benjamin A, Brown R. A nationwide evaluation of spontaneous coronary artery dissection in pregnancy and the puerperium. *Heart*. (2016) 102(24):1974–9. doi: 10.1136/heartjnl-2016-309403

17. Fahmy P, Prakash R, Starovoytov A, Boone R, Saw J. Pre-disposing and precipitating factors in men with spontaneous coronary artery dissection. *JACC Cardiovasc Interventions*. (2016) 9(8):866–8. doi: 10.1016/j.jcin.2016.02.024

18. Havakuk O, Goland S, Mehra A, Elkayam U. Pregnancy and the risk of spontaneous coronary artery dissection: an analysis of 120 contemporary cases. *Circ Cardiovasc Interv*. (2017) 10(3):e004941. doi: 10.1161/CIRCINTERVENTIONS.117.004941

19. Cauldwell M, Steer P, von Klemperer K, Kaler M, Grixti S, Hale J, et al. Maternal and neonatal outcomes in women with history of coronary artery disease. *Heart*. (2020) 106(5):380–6. doi: 10.1136/heartjnl-2019-315325

20. Tweet MS, Best PJ, Hayes SN. Unique presentations and etiologies of myocardial infarction in women. *Curr Treat Options Cardiovasc Med*. (2017) 19:1–12. doi: 10.1007/s11936-017-0571-1

21. Hayes SN, Kim ES, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. Spontaneous coronary artery dissection: current state of the science: a scientific

statement from the American Heart Association. *Circulation*. (2018) 137:e523–57. doi: 10.1161/CIR.0000000000000564

22. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *Br Med J*. (1998) 316(7137):1043. doi: 10.1136/bmj.316.7137.1043

23. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study. *Circulation*. (2006) 113(12):1564–71. doi: 10.1161/CIRCULATIONAHA.105.576751

24. Petitti DB. Combination estrogen–progestin oral contraceptives. *N Engl J Med*. (2003) 349(15):1443–50. doi: 10.1056/NEJMcp030751

25. Giacalone R, Ferretti M, Gurgoglione FL, Vezzani A, Pfleiderer B, De Panfilis C, et al. Assessment of the role of non traditional risk factors on spontaneous coronary artery dissections. *J Clin Cardiol Cardiovasc Interv*. (2022) 5:272. doi: 10.31579/2641-0419/289

26. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. *Circulation*. (2006) 113:898–918. doi: 10.1161/CIRCULATIONAHA.106.171016

27. Sharma S, Kaadan M, Duran J, Ponzini F, Mishra S, Tsiaras S, et al. Risk factors, imaging findings, and sex differences in spontaneous coronary artery dissection. *Am J Cardiol*. (2019) 123(11):1783–7. doi: 10.1016/j.amjcard.2019.02.040

28. Mantzoros CS, Evagelopoulou K, Moses AC. Outcome of percutaneous transluminal coronary angioplasty in patients with subclinical hypothyroidism. *Thyroid*. (1995) 5(5):383–7. doi: 10.1089/thy.1995.5.383

29. Freire SJC, Fernández JFD, Gheorghe LL, Menchero AEG, Jiménez JL, Garrido JR, et al. Spontaneous coronary artery dissection and hypothyroidism. *Rev Esp Cardiol (Engl Ed)*. (2019) 72(8):625–33. doi: 10.1016/j.rec.2018.06.031

30. Chen S, Merchant M, Mahrer KN, Ambrosy AP, Lundstrom RJ, Sahar Naderi M. Pregnancy-associated spontaneous coronary artery dissection: clinical characteristics, outcomes, and risk during subsequent pregnancy. *J Invasive Cardiol*. (2021) 33(6): E457–66. PMID: 34001675

31. Karadag B, Roffi M. Postpartal dissection of all coronary arteries in an in vitro-fertilized postmenopausal woman. *Tex Heart Inst J*. (2009) 36(2):168. PMID: 19436817

32. Paratz ED, Kao C, MacIsaac AI, Somaratne J, Whitbourn R. Evolving management and improving outcomes of pregnancy-associated spontaneous coronary artery dissection (P-SCAD): a systematic review. *IJC Heart Vasc*. (2018) 18:1–6. doi: 10.1016/j.ijcha.2017.12.001

33. Saw J, Aymong E, Sedlak T, Buller C, Starovoytov A, Ricci D, et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv*. (2014) 7 (5):645–55. doi: 10.1161/CIRCINTERVENTIONS.114.001760

34. Allan C, Lainchbury J, Mcalister C, Davison R, Maginness W, Puri A. The role of stress as a precipitating factor in spontaneous coronary artery dissection. *Heart Lung Circ*. (2018) 27:S6–7. doi: 10.1016/j.hlc.2018.05.114

35. Daoulah A, Al-Faifi S, Alsheikh-Ali A, Hersi AS, Lotfi A. Ventricular arrhythmias in patients with spontaneous coronary artery dissection: findings from the gulf spontaneous coronary artery dissection (gulf SCAD) registry. *Crit Pathw Cardiol*. (2020) 19(3):146–52. doi: 10.1097/HPC.0000000000000219

36. Daoulah A, Al-Faifi S, Madan M, Arafat A, Hersi A, Alasmari A, et al. Clinical presentation and outcome of patients with spontaneous coronary artery dissection versus atherosclerotic coronary plaque dissection. *Crit Pathw Cardiol*. (2021) 20 (1):36–43. doi: 10.1097/HPC.0000000000000233

37. Murphy B, Rogerson M, Hesselson S, Iismaa S, Hoover V, Le Grande M, et al. Prevalence of anxiety, depression, and distress in SCAD and non-SCAD AMI patients: a comparative study. *J Cardiopulm Rehabil Prev*. (2023) 10:1097. doi: 10.1097/HCR.0000000000000782

38. Pezzini A, Granella F, Grassi M, Bertolino C, Del Zotto E, Immovilli P, et al. History of migraine and the risk of spontaneous cervical artery dissection. *Cephalalgia*. (2005) 25(8):575–80. doi: 10.1111/j.1468-2982.2005.00919.x

39. Khiatah B, Jazayeri S, Yamamoto N, Burt T, Frugoli A, Brooks DL. Cardiovascular disease in women: a review of spontaneous coronary artery dissection. *Medicine (Baltimore)*. (2022) 101(38):e30433. doi: 10.1097/MD.0000000000030433

40. Daoulah A, Al-Faifi S, Alhamid S, Youssef A, Alshehri M, Al-Murayeh M, et al. Spontaneous coronary artery dissection in the gulf: g-SCAD registry. *Angiology*. (2021) 72(1):32–43. doi: 10.1177/0003319720946974

41. Fontanelli A, Benettin A, Bonanno C, Cabianca E, Desideri A, Santarelli A, et al. Spontaneous dissections of coronary arteries (SCAD) and acute coronary syndromes (ACS). Preliminary Results of the DISCOVERY-ACS: a Multicenter Prospective Registry with a Patients-Control Group (2008).

42. Yang C, Alfadhel M, Saw J. Spontaneous coronary artery dissection: latest developments and new frontiers. *Curr Atheroscler Rep*. (2020) 22:1–8. doi: 10.1007/s11883-020-00866-4

43. Shamloo B, Chintala R, Nasur A, Ghazvini M, Shariat P, Diggs J, et al. Spontaneous coronary artery dissection: aggressive vs. conservative therapy. *J Invasive Cardiol*. (2010) 22(5):222–8. PMID: 20440039

44. Regragui H, Boussaadani B, Sasbou L, Bouhdadi H, Wazaren H, Cherti M. Conservative management of spontaneous coronary artery dissection: a case report. *Pan African Medical Journal*. (2020) 36(1):334. doi: 10.11604/pamj.2020.36.334.25546

45. Bocchino PP, Angelini F, Franchin L, D'Ascenzo F, Fortuni F, De Filippo O, et al. Invasive versus conservative management in spontaneous coronary artery dissection: a meta-analysis and meta-regression study. *Hellenic J Cardiol*. (2021) 62 (4):297–303. doi: 10.1016/j.hjc.2021.02.013

46. Modaragamage Dona AC, Abuelgasim E, Abuelgasim B, Kermali M, Zahra SA, Hewage S, et al. Dissection of coronary artery: a clinical overview. *J Cardiol*. (2021) 77 (4):353–60. doi: 10.1016/j.jjcc.2020.08.011

47. Adlam D, Alfonso F, Maas A, Vrints C, Committee W. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J*. (2018) 39(36):3353. doi: 10.1093/eurheartj/ehy080

48. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *J Am Coll Cardiol*. (2008) 52(3):171–80. doi: 10.1016/j.jacc.2008.03.049

49. Qasqas SA, McPherson C, Frishman WH, Elkayam U. Cardiovascular pharmacotherapeutic considerations during pregnancy and lactation. *Cardiol Rev*. (2004) 12(4):201–21. doi: 10.1097/01.crd.0000102420.62200.e1

50. Appleby CE, Barolet A, Ing D, Ross J, Schwartz L, Seidelin P, et al. Contemporary management of pregnancy-related coronary artery dissection: a single-centre experience and literature review. *Exp Clin Cardiol*. (2009) 14(1): e8–e16. PMID: 19492033

51. Alfonso F, Paulo M, Lennie V, Dutary J, Bernardo E, Jiménez-Quevedo P, et al. Spontaneous coronary artery dissection: long-term follow-up of a large series of patients prospectively managed with a "conservative" therapeutic strategy. *JACC Cardiovasc Interv*. (2012) 5(10):1062–70. doi: 10.1016/j.jcin.2012.06.014

52. Lee R, Carr D. Pregnancy-associated spontaneous coronary artery dissection (PASCAD): an etiology for chest pain in the young peripartum patient. *CJEM*. (2018) 20(S2):S64–9. doi: 10.1017/cem.2018.9

53. Cerrato E, Giacobbe F, Quadri G, Macaya F, Bianco M, Mori R, et al. Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry. *Eur Heart J*. (2021) 42 (33):3161–71. doi: 10.1093/eurheartj/ehab372

54. Vijayaraghavan R, Verma S, Gupta N, Saw J. Pregnancy-related spontaneous coronary artery dissection. *Circulation*. (2014) 130(21):1915–20. doi: 10.1161/CIRCULATIONAHA.114.011422

55. Hussein MT E, Blayney S. Spontaneous coronary artery dissection: a comprehensive overview. *J Emerg Nurs*. (2020) 46(5):701–10. doi: 10.1016/j.jen.2020.05.012

56. Gilhofer TS, Saw J. Spontaneous coronary artery dissection: a review of complications and management strategies. *Expert Rev Cardiovasc Ther*. (2019) 17 (4):275–91. doi: 10.1080/14779072.2019.1598261

57. Hayes SN, Tweet MS, Adlam D, Kim ES, Gulati R, Price JE, et al. Spontaneous coronary artery dissection: JACC state-of-the-art review. *J Am Coll Cardiol*. (2020) 76 (8):961–84. doi: 10.1016/j.jacc.2020.05.084

58. Feldbaum E, Thompson E, Cook T, Sanghavi M, Wilensky R, Fiorilli P, et al. Management of spontaneous coronary artery dissection: trends over time. *Vasc Med*. (2023) 28(2):131–8. doi: 10.1177/1358863X231155305

59. Tweet MS, Gulati R. Chapter 5 – spontaneous coronary artery dissection. In: Aggarwal NR, Wood MJ, editors. *Sex Differences in Cardiac Diseases, Elsevier* (2021). p. 75–92. doi: 10.1016/B978-0-12-819369-3.00026-5

60. Tweet MS, Gulati R, Hayes SN. What clinicians should know about spontaneous coronary artery dissection. *Mayo Clin Proc*. (2015) 90(8):1125–30. doi: 10.1016/j.mayocp.2015.05.010

61. Vautrin E, Jean A, Fourny M, Marlière S, Vanzetto G, Bouvaist H, et al. Sex differences in coronary artery lesions and in-hospital outcomes for patients with ST-segment elevation myocardial infarction under the age of 45. *Catheter Cardiovasc Interv*. (2020) 96(6):1222–30. doi: 10.1002/ccd.28627

62. Tweet MS, Young KA, Best PJ, Hyun M, Gulati R, Rose CH, et al. Association of pregnancy with recurrence of spontaneous coronary artery dissection among women with prior coronary artery dissection. *JAMA network Open*. (2020) 3(9):e2018170. doi: 10.1001/jamanetworkopen.2020.18170

Appendix 1

Search history on Medline 04/04/2023

Search number	Query	Sort by	Filters	Search details	Results	Time
5	((Spontaneous coronary artery dissection) OR (non-atherosclerotic coronary artery dissection)) AND (female)			((("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields])) OR ("non-atherosclerotic"[All Fields] AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]))) AND ("femal"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "female s"[All Fields] OR "femals"[All Fields])	1,198	03:24:32
4	Non atherosclerotic coronary artery dissection			"non"[All Fields] AND ("atherosclerotic"[All Fields] OR "atherosclerotically"[All Fields] OR "atherosclerotics"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields])	152	03:07:05
3	(Spontaneous coronary artery dissection) AND (female)			("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]) AND ("femal"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "female s"[All Fields] OR "femals"[All Fields])	1,191	03:06:00
2	(Spontaneous coronary artery dissection) AND (pregnancy)			("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])	298	03:05:27
1	Spontaneous coronary artery dissection			("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields])	2,046	03:04:43

Search history on Medline 07/06/2023.

Search number	Query	Sort by	Filters	Search details	Results	Time
9	(((Spontaneous coronary artery dissection) AND ((pregnancy) OR (postpartum) OR (peripartum))) NOT ((case report) OR (review))			(("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancys"[All Fields] OR ("postpartum period"[MeSH Terms] OR ("postpartum"[All Fields] AND "period"[All Fields]) OR "postpartum period"[All Fields] OR "postpartum"[All Fields]) OR ("peripartum period"[MeSH Terms] OR ("peripartum"[All Fields] AND "period"[All Fields]) OR "peripartum period"[All Fields] OR "peripartum"[All Fields])) NOT ("case reports"[Publication Type] OR "case report"[All Fields] OR ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]))	97	13:24:27
8	(((Spontaneous coronary artery dissection) AND ((pregnancy) OR (postpartum) OR (peripartum))) NOT (case report)			(("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancys"[All Fields] OR ("postpartum period"[MeSH Terms] OR ("postpartum"[All Fields] AND "period"[All Fields]) OR "postpartum period"[All Fields] OR "postpartum"[All Fields]) OR ("peripartum period"[MeSH Terms] OR ("peripartum"[All Fields] AND "period"[All Fields]) OR "peripartum period"[All Fields] OR "peripartum"[All Fields])) NOT ("case reports"[Publication Type] OR "case report"[All Fields])	172	13:23:36
7	(((Spontaneous coronary artery dissection) AND ((pregnancy) OR (postpartum))) NOT (case report)			(("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancys"[All Fields] OR ("postpartum period"[MeSH Terms] OR ("postpartum"[All Fields] AND "period"[All Fields]) OR "postpartum period"[All Fields] OR "postpartum"[All Fields])) NOT ("case reports"[Publication Type] OR "case report"[All Fields])	148	13:18:40
6	((Spontaneous coronary artery dissection) AND ((pregnancy) OR (postpartum))			("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancys"[All Fields] OR ("postpartum period"[MeSH Terms] OR ("postpartum"[All Fields] AND "period"[All Fields]) OR "postpartum period"[All Fields] OR "postpartum"[All Fields]))	401	13:17:43
5	((Spontaneous coronary artery dissection) AND (pregnancy)) OR (postpartum)			(("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancys"[All Fields])) OR ("postpartum period"[MeSH Terms] OR ("postpartum"[All Fields] AND "period"[All Fields]) OR "postpartum period"[All Fields] OR "postpartum"[All Fields])	132,274	13:17:13
4	(Spontaneous coronary artery dissection) NOT (postmenopausal period)			(("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields])) NOT ("postmenopause"[MeSH Terms] OR "postmenopause"[All Fields] OR ("postmenopausal"[All Fields] AND "period"[All Fields]) OR "postmenopausal period"[All Fields])	2,065	13:16:19
3	Spontaneous coronary artery dissection AND postpartum			("spontaneous"[All Fields] OR "spontaneously"[All Fields]) AND ("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND ("dissect"[All Fields] OR "dissected"[All Fields] OR "dissecting"[All Fields] OR "dissection"[MeSH Terms] OR "dissection"[All Fields] OR "dissections"[All Fields] OR "dissects"[All Fields]) AND ("postpartum period"[MeSH Terms] OR ("postpartum"[All Fields] AND "period"[All Fields]) OR "postpartum period"[All Fields] OR "postpartum"[All Fields])	222	13:14:09

(*Continued*)

Continued

Search number	Query	Sort by	Filters	Search details	Results	Time
2	(Spontaneous coronary artery dissection) AND (pregnancy)			(“spontaneous"[All Fields] OR “spontaneously"[All Fields]) AND (“coronary vessels"[MeSH Terms] OR (“coronary"[All Fields] AND “vessels"[All Fields]) OR “coronary vessels"[All Fields] OR (“coronary"[All Fields] AND “artery"[All Fields]) OR “coronary artery"[All Fields]) AND (“dissect"[All Fields] OR “dissected"[All Fields] OR “dissecting"[All Fields] OR “dissection"[MeSH Terms] OR “dissection"[All Fields] OR “dissections"[All Fields] OR “dissects"[All Fields]) AND (“pregnancy"[MeSH Terms] OR “pregnancy"[All Fields] OR “pregnancies"[All Fields] OR “pregnancys"[All Fields])	302	13:13:16
1	Spontaneous coronary artery dissection			(“spontaneous"[All Fields] OR “spontaneously"[All Fields]) AND (“coronary vessels"[MeSH Terms] OR (“coronary"[All Fields] AND “vessels"[All Fields]) OR “coronary vessels"[All Fields] OR (“coronary"[All Fields] AND “artery"[All Fields]) OR “coronary artery"[All Fields]) AND (“dissect"[All Fields] OR “dissected"[All Fields] OR “dissecting"[All Fields] OR “dissection"[MeSH Terms] OR “dissection"[All Fields] OR “dissections"[All Fields] OR “dissects"[All Fields])	2,074	13:12:38

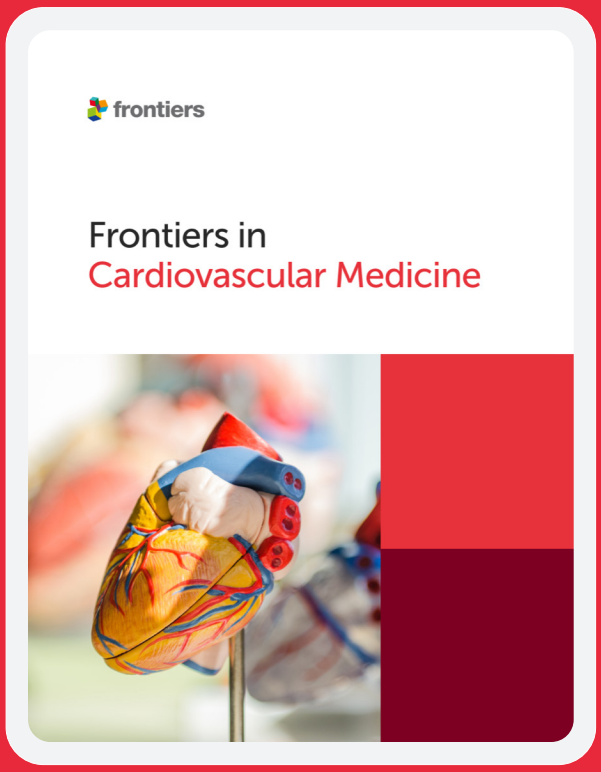
Frontiers in
Cardiovascular Medicine

Innovations and improvements in cardiovascular treatment and practice

Focuses on research that challenges the status quo of cardiovascular care, or facilitates the translation of advances into new therapies and diagnostic tools.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact