Treatment of Spontaneous Coronary Artery Dissection by Bio-resorbable Vascular Scaffolds

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SUMMARY

BACKGROUND

Spontaneous coronary artery dissection (SCAD) is a rare, but perhaps underestimate cause of acute coronary syndrome, and recent studies reported a surge in the recognition of this condition, particularly in young women presenting with acute coronary syndrome. However, despite the latest insights in epidemiological knowledge and advance in diagnostic capability using intracoronary tomographic imaging, the management of SCAD remains unsettled. Bioresorbable vascular scaffold (BRS) might represent an attractive therapeutic tool in SCAD, allowing for transient sealing of intimal flap and scaffolding of intramural hematoma, overcoming late pathology related to metallic stent. At the same time, BRS implantation could reduce the risk of late malapposition due to intramural hematoma reabsorption. The aim of this study was to investigate feasibility and safety of BRS in SCAD.

METHODS

In a multicenter prospective registry, 27 patients affected by SCAD presenting with ACS and treated by BRS between 2013 and 2015 were included. Diagnosis of SCAD was based on angiography when pathognomonic angiographic appearance with contrast dye staining of the

arterial wall with multiple radiolucent lumens was appreciated (type I of Saw Classification);

smooth and diffuse narrowing with abrupt change in arterial caliber, with demarcation from normal

diameter to diffuse narrowing, or long and linear stenosis, or hazy long lesions (type II and III of

Saw classification) were considered as SCAD, especially in absence of atherosclerotic changes in

the other vessels and high clinical suspicion of SCAD; when angiography was considered

inconclusive diagnosis was definitely accomplished by IVUS Inclusion criteria were: SCAD with

ongoing ischemia, or flow-limiting, or severe lumen narrowing and proximal location, visual

estimated RVD ≥ 2.5 mm ≤ 4.0 mm. Exclusion criteria were: pregnancy, contraindication to DAPT,

hyper-reactivity to poly-lactate. In SCAD type II and III, IVUS/OCT was strongly suggested to

confirm diagnosis. Angiographic success was defined as successful delivery of BRS at intended

target lesion with TIMI-3 flow and stenosis <30%; clinical procedural success (patient level) as

angiographic success without the occurrence of cardiac death, myocardial infarction/re-infarction or

target vessel revascularization (TVR) during the hospital stay. Clinical plus CT-scan or angiography

was planned at 12-months follow-up.

RESULTS

All but 2 patients were female, mean age 48±9 years; risk factors for SCAD were identified in 14 patients. Presentation was STEMI (48%), NSTE-ACS (37%), or life-threatening arrhythmias (15%). LAD was the most common culprit vessel (69%); 2 patients underwent BRS on 2 vessels: thus, 29 coronary arteries were treated. Revascularization was accomplished with 1 to 5 BRS per patient (mean total scaffold length 57±28 mm). IVUS guidance was used in 45%, post-dilatation in 72%. Device success was obtained in 100% of cases. Angiographic success was achieved in 28 of 29 (97%) lesions. Procedural success was achieved in 25 of 27 (93%) patients. No in-hospital deaths or non-fatal myocardial re-infarction were observed; 1 patient underwent TVR due to symptomatic SCAD progression at scaffolds' edge. At 1-year follow-up, 1 TVR due to asymptomatic BRS recoil was observed. Coronary imaging (either invasive or not invasive) follow-up was performed in 15 patients with 1 year follow up showing BVS patency in 14 of 15 cases; one case of recurrent SCAD and one case of SCAD persistence were registered.

CONCLUSIONS

Our study, on the largest cohort of patients to date, suggests the feasibility and safety of bio-resorbable coronary scaffolds in Spontaneous Coronary Artery Dissection, with high rates of

angiographic and procedural success, and favorable 1-year results. Nevertheless, longer evaluation

in larger studies is needed.

Introduction

Spontaneous coronary artery dissection (SCAD) has long been recognized as a cause of acute coronary syndromes (ACS). Initially considered very rare and associated primarily with pregnancy and the peri-partum period, the increasing use of higher sensitivity Troponin assays and early angiography and introduction of intracoronary imaging techniques in ACS has led to increased diagnosis. Thus, it is now recognized that SCAD represents a significant cause of ACS in predominantly young to middle-aged women, with most cases occurring outside the context of recent pregnancy. Knowledge has further advanced in the last 5-years as a result of an international research effort primarily focused on building and studying national SCAD registries. These studies have demonstrated, not only that SCAD is a distinct pathophysiological entity, but that there are key differences in management and outcomes compared to ACS of atherosclerotic etiology.

However, despite the latest insights in epidemiological knowledge and advance in diagnostic capability using intracoronary tomographic imaging, the management of SCAD remains unsettled.

1.1 DEFINITION

Spontaneous coronary artery dissection (SCAD) refers to the acute development of a false lumen within the coronary artery wall, which may compromise coronary flow by external compression of the true lumen. Dissections arising from instrumentation (iatrogenic) during coronary procedures, blunt trauma and as a consequence of a penetrating ulcer secondary to atherosclerotic disease are not considered as primary SCAD. Furthermore, contemporary usage of the term SCAD is typically reserved for the non-atherosclerotic variant, and most modern series exclude SCAD due to atherosclerotic coronary artery disease.

2. PATHOLOGY

SCAD is a recognized cause of sudden cardiac death, presumably as a result of ventricular arrhythmia triggered by myocardial ischemia or infarction. Accurate diagnosis at autopsy can be challenging and the condition is likely under-represented in post mortem series (1,2). A high index of suspicion for SCAD is recommended in all potential cases with careful assessment of coronary histopathology, particularly of the mid-distal vessels which are predominantly affected in SCAD. SCAD results from the development of a false lumen, generally in the outer third of the tunica media, and/or between tunica media and avventitia (1-17). The primary cause of false lumen

formation is still unclear with two potential mechanisms proposed: the 'inside-out' model, where

the key event is the development of a discontinuity or 'tear' in the endothelium and intimal,

allowing blood to entry the internal elastic lamina and accumulate in the media; and the 'outside-in'

mechanism where the causal event is the primary disruption of a vasa vasorum micro-vessel leading

to hemorrhage directly into the tunica media (18, 19 20). In either case blood propagates axially as

the false lumen extends leading to compression of the true lumen. It remains unclear if there is a

single dominant mechanism in SCAD or if both causal events are possible. However a recent

intracoronary imaging study with high resolution optical coherence tomography (OCT) evidence

has shown case examples where there is no demonstrable communication between false and true

lumens (21-23), suggesting the 'outside-in' mechanism is likely in at least some cases.

Histologically, fibrin-rich hematoma is present in the false lumen with a neutrophil infiltrate

extending into the media. There are frequent reports of a peri-adventitial inflammatory infiltrate

with a predominance of eosinophils (1, 5-7, 9, 10, 13, 14, 17, 24). Some early cases report features

of cystic medial necrosis (25-27), however in recent reports and series it was not reported (5,7,8).

Significant co-existent atherosclerotic coronary artery disease in SCAD is uncommon.

3. EPIDEMIOLOGY

3.1 Incidence

The true incidence of spontaneous coronary artery dissection (SCAD) is unknown, as this condition remains probably under-diagnosed (28). SCAD was historically considered a very rare condition, however contemporary series report SCAD diagnosis rates of 0.2%-0.7% of all angiograms and 2-4% of angiograms performed in the context of ACS (29-31). Furthermore, in younger women SCAD is reported to account for a much higher proportion of ACS presentations: in a Canadian series of women less than 50 years with myocardial infarction, SCAD accounted for 24% of cases (32). Likewise a Japanese registry reported SCAD in 35% of females patients under 50 years presenting with acute myocardial infarction (33), a French series reported SCAD in 36% of women under 60 years with ACS and one or fewer conventional cardiovascular risk factors (23) and a smaller Australian series describes a SCAD prevalence of 23% in women under 60 years presenting with ACS (34). SCAD during pregnancy and peripartum period account for a minority of these cases (around 10% in most contemporary series) (23, 30, 33-46), thus SCAD is currently no longer considered predominantly a peripartum condition. However, 21-27% of myocardial infarctions in pregnancy and 50% of postpartum coronary events are reportedly due to SCAD (45,47).

3.2. Demographics

Previously considered primarily a disease of young females, SCAD has now been described in patients aged 18 to 84 years (35,39) with the mean age in the most contemporary series ranging from 44 to 53 years (23,30,33,34,36,38,39,41-44,46,48). No ethnic variations have been reported but there is a strong female predominance.

4. PATHOPHYSIOLOGY: RISK FACTORS AND ASSOCIATIONS

The pathophysiology of SCAD remains largely unknown. It is likely that a combination of predisposing factors increase susceptibility such that a relatively minor trigger event is sufficient to precipitate SCAD. There are a large number of reported associations with SCAD (6, 26, 35, 39, 42,49-51), some of which (e.g. female sex, pregnancy and fibromuscular dysplasia (FMD) present a well-established relationship with SCAD in multiple series. Other associations are based on anecdotal case reports and in this context causality is harder to determine.

4.1 Female sex and pregnancy

The vast majority of SCAD patients (~90%) are women (30,33,34,36,38-45,49,50) There is some evidence from a Canadian series that male SCAD patients are different from female cases, being slightly younger and with higher rates of preceding isometric exercise and lower prior emotional stress levels. The predilection of SCAD for female patients, as well as the association with pregnancy has traditionally suggested a pathophysiological role for female sex hormones. The specific nature of this association remains to be elucidated but may relate to hormonal influences on vascular connective tissue and/or the vessel microvasculature. Data from most contemporary SCAD series suggest that pregnancy-associated SCAD represents approximately 10% of SCAD cases.

Multi-parity may increase risk (37) Pregnancy-related SCAD has been reported antepartum as early as the 5th week of pregnancy (52) although most pregnant cases occur in the third trimester (53,55). It also occurs in the early (<6 weeks), late (6 weeks to 12 months) and very late postpartum (12 to 24 month) periods, with the peak occurring in the early postpartum period (53-55). Anecdotally, late postpartum SCAD may occur in association with breastfeeding. A Canadian study identified (56). Pregnancy-related SCAD cases from a nationwide cohort study of 4.4 million pregnancies between 2008 and 2012 (incidence 1.8 SCAD cases per 100000 pregnancies) (40), a higher incidence of pregnancy-related SCAD compared to the historical literature. This study suggested

the P-SCAD presentation may be more severe than SCAD outside the context of pregnancy, with

STEMI in 64%, cardiogenic shock in 24%, cardiac arrest in 14% and maternal death in 4.5%.

Moreover, pregnancy-related SCAD was more likely to involve the proximal coronaries and was

associated with a reduction in post-infarct ejection fraction. The findings of a more severe

pregnancy-related SCAD phenotype were confirmed in an analysis of contemporary published

cases (55) and a small retrospective study comparing (7) pregnancy-related SCAD and 16 SCAD

cases (48).

4.2 Fibromuscular dysplasia

SCAD has been associated with various predisposing arteriopathies (19,28). The most

frequent is fibromuscular dysplasia (FMD), a non-atherosclerotic, non-inflammatory disease of

arterial walls, which also occurs predominantly in middle-aged females with few cardiovascular

risk factors. FMD may lead to stenosis, dissections and aneurysms of medium-sized arteries,

including but not limited to renal, cervico-cephalic and visceral arteries (57,58). It is currently

classified by angiography into two subtypes, multifocal and (uni)focal. Multifocal FMD, with the

typical 'string-ofbeads' pattern, is the angiographic presentation of medial FMD and is at least four

times more frequent than unifocal FMD (58-60). Since the first case series reporting the association

of SCAD with extra-coronary FMD in 2012, (61,62) FMD of extra-coronary vascular beds has been

documented in 11-86% of patients with SCAD (35,39,42,51,54,63-65).

The prevalence of extra-coronary FMD in various cohorts (Figure 4) may differ according to the

proportion of patients screened, and mainly the screening protocol used (e.g. imaging technique,

vascular beds). In current series, the most commonly affected vascular beds are renal, cervico-

cephalic and iliac arteries (39, 54, 63-65). Besides typical FMD lesions, other extra-coronary

vascular abnormalities (EVAs) such as aneurysms, dissections, irregularities, undulations and/or

tortuosity have been reported (63,64). Whether the latter correspond to subtle forms of FMD or a

different process such as a form of connective tissue disorder remains to be established (64).

4.3 Hormonal therapy

Long-term exposure to exogenous estrogen or progesterone is postulated to cause similar long-term

changes in coronary arterial architecture, and it is believed to be an important risk factor for SCAD

(66-68). In a presented series of 215 SCAD patients, 12.4% were actively on hormone replacement

therapy, and these patients had higher recurrent MI (29.2% vs. 6.5%; p 0.03) on follow-up

compared with those not on hormone replacement therapy (69).

4.4 Inflammatory conditions

Several chronic systemic inflammatory conditions were reported to be potentially associated with SCAD, although most of these were only case reports, and the pathophysiological links were not established. The prevalence of concomitant systemic inflammatory disease was 8.9% in the 168 patient series. In a smaller series by Alfonso et al. (67), 27 patients diagnosed with isolated SCAD underwent laboratory screening for inflammatory and immunologic markers; however, none were diagnosed with systemic inflammation on screening. This is in keeping with the observation that the incidence of acute inflammation associated with SCAD was very low (<1%) (68). The link between systemic inflammation and SCAD is suspected to be due to chronic inflammation from vasculitis (70).

4.5 Connective tissue disorders

Several connective tissue disorders have also been associated with SCAD, most notably Marfan and Ehler-Danlos type 4 syndromes. However, the reported frequency of these associated connective tissue conditions is infrequent (1% to 2%) (68,71). Thus, although many of these disorders can be identified on genetic screening, the yield is low unless patients have clear clinical characteristics suggestive of these disorders.

4.6 Triggers and Precipitating Factors

Precipitating stressors that result in a Valsalva-like increase in thoracoabdominal pressure or that raise catecholamines can increase cardiocirculatory shear stress, which can trigger SCAD, especially in patients with underlying predisposing arteriopathies. Several stressors have been reported in literature, including intense emotional stress, physical activities (especially isometric exercises), hormonal therapy, sympathomimetic drugs, and intense Valsalva-like activities (e.g., childbirth, coughing, retching, vomiting, bowel movement) (72-78). Emotional stress is speculated to have a different pathophysiological trigger, presumably related to stress catecholamines. A catecholamine surge may increase myocardial contractility or vasospasm, which can increase arterial shear stress, leading to intimal rupture or disruption of the vasa vasorum (74). Acute exposures to high-dose hormonal therapy (e.g., injections of beta-human chorionic gonadotropin, corticosteroids) have also been implicated as triggers for SCAD, potentially through accelerated arterial architectural disruption or hemodynamic stress (76-78). In a prospective cohort, as many as 57% of patients reported precipitating stressors preceding their SCAD event; 40% reported having severe emotional stress, and 24% reported significant physical activities (74). Men and women have different prevalences of predisposing and precipitating factors. In a recent paper, men were more

likely to report isometric exercises, but were less likely to report emotional stressors compared with women (79).

5. CLINICAL PRESENTATION

There is a wide spectrum of clinical presentations and severity of SCAD. Almost all patients with SCAD present with ACS and elevation of cardiac enzymes (74,80-82). The proportion who presented with STEMI varied widely in different series, ranging from 24% to 87% (74,80-82). A small proportion can be complicated with ventricular arrhythmias (3% to 10%) (74,80,83), cardiogenic shock (<3%) (74,80), or sudden cardiac death. Sudden death may be underestimated in SCAD, since many of these cases fall before hospital admission (84). Chest discomfort is the most common presenting symptom, less frequent symptoms included radiation to the arms or neck, nausea or vomiting, diaphoresis, dyspnea, and back pain. Overall, w34% of SCAD patients had unstable symptoms (ongoing pain and/or ischemia or stuttering and/or recurrent pain that required medications for pain relief) before arrival at the catheterization laboratory. Generally, Troponin levels and cardiac markers of necrosis, are increased, however there is a wide variation in elevation of cardiac enzyme levels, reflecting a wide range of jeopardize myocardium and residual flow condition.

6. DIAGNOSIS OF SCAD

Accurate and early diagnosis of SCAD is a key because the management and investigation of

SCAD is different from atherosclerotic disease. Coronary angiography is widely available and is the

first-line imaging for patients presenting with ACS. However, coronary angiography has significant

limitations in diagnosing SCAD because it is a 2-dimensional "luminogram" that does not image

the arterial wall. Dedicated intracoronary imaging (OCT and intravascular ultrasound [IVUS]) that

images the arterial wall layers improves SCAD diagnosis, but it is not as widely available and is

associated with additional risks and costs. Thus, coronary angiography remains instrumental in

SCAD diagnosis, and angiographers should gain familiarity with the angiographic variants of

SCAD. The conventional angiographic description of SCAD includes the appearance of

extraluminal contrast staining, multiple radiolucent lumens, spiral dissection, and intraluminal

filling defects (85). However, such descriptions and the National Heart, Lung, and Blood Institute

classification for coronary dissections were devised in the pre-stent era for angioplasty-induced

dissections. The predominant angiographic appearance of SCAD consists of smooth narrowing of

varying severity and length due to IMH. Thus, a SCAD angiographic classification was described to

better characterize the appearance (86). More recently, an angiographically classification of SCAD has been introduced by Saw and coworkers.

Type 1 describes the pathognomonic appearance of arterial wall contrast staining with multiple radiolucent lumens. Type 2 describes diffuse stenosis of varying severity and length (typically >20 mm), and with appreciable, but often subtle, abrupt changes in the arterial caliber from the normal diameter to diffuse smooth narrowing. This diffuse narrowing may be bordered by normal artery segments that are proximal and distal to the IMH (type 2A variant), or it may extend to the apical tip of the artery (type 2B variant) (87). Type 3 describes focal or tubular (typically <20 mm) stenosis that mimics atherosclerosis, which requires intracoronary imaging to confirm diagnosis. A simple algorithm to aid the diagnosis of SCAD was proposed together with this classification (Figure 4) (86). Using this classification, the most common SCAD angiographic appearance was type 2 in 67.5% of cases (137 of 203), followed by type 1 in 29.1% (59 of 203), and type 3 in 3.4% (7 of 203) (9). Other investigators have also reported diffuse smooth stenosis to be the most common angiographic manifestation (13,15,28).

These findings highlight the importance of familiarity with the nonpathognomonic variants of SCAD (types 2 and 3) to improve diagnosis. The type 2 variants are associated with very long lengths of narrowing and can be readily identifiable as SCAD after familiarity with this appearance;

however, intracoronary imaging or CT-scan in case of distal lesions should be considered if the diagnosis is uncertain. The type 2B variant may be mistaken as "normal vessel tapering," but there is usually a discernible demarcation from a normal vessel to stenosis. The type 3 variant may be significantly underdiagnosed, and may be mistaken for atherosclerotic disease if intracoronary imaging is not performed (87). Any coronary artery can be affected by SCAD, with the left anterior descending artery being the most commonly involved (34% to 42%) (74,80,81). Overall, the left anterior descending artery and its branches (diagonal or septal) are affected in 45% to 61%, the circumflex and branches (ramus, obtuse marginal) in 15% to 45%, the right coronary artery and branches (acute marginal, posterior descending, posterolateral) in 10% to 39%, and the left main in 0% to 4% of cases (74,80,81,82,88). Most dissections affected the mid to distal segments, with <10% affecting the proximal left anterior descending, circumflex, right coronary, or left main arteries (74). Multiple arteries were dissected in 9% to 19% of cases, and noncontiguous >1 artery dissections occurred in 5% to 10% of cases (74,80,81,82,88).

7. INTRACORONARY IMAGING

7.1 Intravascular UltraSound and Optical Coherence Tomography

Both OCT and IVUS provide complementary details to diagnose SCAD, which requires the

presence of IMH or a double lumen (Figure 5) (28). OCT has a superior spatial resolution of 10 to

20 mm versus IVUS, with lower resolution (150 mm), but better penetration. For SCAD imaging,

OCT is superior for visualizing intimal tears, intraluminal thrombi, false lumens, and IMH, but it is

limited by optical penetration and shadowing, and may not depict the entire depth of the IMH.

IVUS has adequate resolution to visualize IMH and false lumens, but the lumen intimal interface is

not as clearly delineated as with OCT. IVUS does provide deeper vessel visualization with better

ultrasound penetration, allowing better appreciation of the extent of IMH. Overall, OCT is preferred

for imaging SCAD due to its superiority and ease in visualizing IMH, intimal disruption, and

double lumens, especially because there is no clinical need to evaluate the full depth and extent of

IMH. Moreover, OCT is superior in visualizing stent strut apposition, thus allowing stent

optimization if intervention is pursued. However, there are potential risks with intracoronary

imaging in the setting of SCAD, including the risks of extending dissection with the wire or

imaging catheter, hydraulic extension with OCT contrast injection, catheter-induced occlusion, and

guide catheter iatrogenic dissection. Thus, the utmost care and meticulous techniques should be

used when performing intracoronary imaging.

7.2 Cardiac CTA.

Cardiac CTA has much lower spatial resolution compared with conventional angiography and has

challenges in evaluating the lumens and walls of small coronary arteries (especially those < 2.5 mm

diameter). Because most of SCAD affects non-proximal arteries and does not have extraluminal

contrast staining, cardiac CTA has limited capacity to diagnose SCAD. Moreover, the often subtle

demarcation from normal to stenosis observed on coronary angiography is frequently not

appreciated on cardiac CTA. Thus, despite its noninvasiveness, cardiac CTA is not recommended

as a first-line imaging for SCAD due to the concerns of missed diagnoses in small and non-

proximal arteries (89). However, it may be useful as an alternative to angiography to assess for

arterial healing after SCAD of larger proximal-mid arteries. In a small series of 34 patients, 24

patients underwent cardiac CTA at a median of 4 months, and complete healing was observed in

83% (14).

8. TREATMENT

The optimal management of SCAD remains undetermined because no randomized trials have compared medical therapies or revascularization strategies, unlike atherosclerotic disease. Standard guideline indicated medical therapies administered for ACS have not been specifically studied for SCAD, and it is unclear if they are beneficial in this unique population (90). Current recommendations on management are largely used on the basis of expert opinions from observational series (89,91,92).

An overall conservative approach is preferred on the basis of expert opinions derived from observational data (2,8–11). This recommendation relies on observations that SCAD arteries heal spontaneously in most cases, and that revascularization is associated with high failure rates.

Although conservative therapy is usually recommended, nevertheless, a small proportion of patients should be considered for revascularization, including those with ongoing or recurrent ischemia, hemodynamic instability, ventricular arrhythmias, or left main dissection.

PCI should be performed in these cases if the anatomy is suitable; otherwise, coronary artery by-pass grafting (CABG) should be considered. However, several series have reported poor technical success with PCI for SCAD. In the Vancouver cohort of 168 patients, successful or partially

successful PCI was achieved in only 64% (57% had extension of dissections during PCI, 12% required urgent CABG, and 6% had stent thrombosis), with long-term durable results in only 30% (74). In the Mayo Clinic series of 189 patients, PCI failure occurred in 53%, and emergency CABG was required in 13% (83). In the Italian series of 134 patients, successful PCI was achieved in 72.5% (9% required urgent CABG, and 5% had stent thrombosis), and patients treated conservatively had lower in-hospital major cardiac adverse events (MACEs) compared with those treated with revascularization (3.8% vs. 16.1%; p ¼ 0.028) (80).

These suboptimal results are a consequence of multiple challenges with PCI in this anatomy. These arteries are typically architecturally weakened by the underlying arteriopathies, and are prone to iatrogenic dissections and extension of dissections during PCI. In a retrospective review of 348 angiographic studies in SCAD patients, iatrogenic catheter-induced dissections occurred in 3.4% (in addition to their presenting SCAD arteries), with a much higher occurrence in ad hoc PCI cases (14.3%) (93). Thus, PCI has to be undertaken cautiously with meticulous techniques, but may still result in suboptimal outcomes. It may be challenging to enter the true lumen with the coronary guidewire, especially in the presence of type 1 angiographic SCAD with intimal disruption. With wiring, angioplasty, or stenting, the IMH can often propagate anterogradely or retrogradely, further compromising the true lumen and extending the dissection. Long stents are typically required

because dissections are extensive, with a higher risk of restenosis. Furthermore, SCAD often involves distal coronary segments that are too small for stents. Moreover, with the natural resorption of IMH over time, there may be subacute and late strut malapposition, which can increase the risk of stent thrombosis (94).

Thus, the role of coronary revascularization remains controversial in SCAD, since CABG demonstrated poor procedural and long-term results, with a low graft patency rate (95), while percutaneous revascularization with coronary stent implantation showed suboptimal angiographic and procedural success in several series (82, 96). In fact, although metallic stents are able to restore vessel patency, in a significant rate of cases anterograde flow still results suboptimal, largely because of propagation of intramural hematoma and/or inadequate coverage of lesion (97).

Notwithstanding, full lesion coverage often requires long and multiple stents, potentially leading to flow degradation, as result of excessive caging of the vessel with altered vasomotion.

 Moreover, long term outcome of patients who underwent PCI and stenting (either BMS or DES) may be affected by stent-induced pathology, such as persisting inflammation and late malapposition, potentially leading to stent thrombosis and late catch-up phenomenon (98-100).

Bioresorbable vascular scaffold (BVS) might represent an attractive therapeutic tool in SCAD, allowing for transient sealing of intimal flap and scaffolding of intramural hematoma, overcoming

late pathology related to metallic stent. At the same time, BVS implantation could reduce the risk of

late malapposition due to intramural hematoma reabsorption. However, thus far the use of BVS in

SCAD is limited to case reports and one small retrospective cohort (101-104).

AIMS

The aim of present study is to assess the feasibility and safety of BVS implantation in SCAD

management.

Methods

Patient population.

The study is based on a multicenter prospectively designed registry including patients affected by

SCAD treated with BVS, retrospectively or prospectively identified, recruited at 12 Italian

Hospitals, according to a pre-specified protocol. Inclusion criteria for enrollment in the registry

were: 1) acute coronary syndrome, or cardiac arrest due to ventricular tachycardia/fibrillation at

hospital admission; and 2) diagnosis of SCAD, based on angiography and Intracoronary Vascular

Ultrasound (IVUS) in case of inconclusive angiography; and 3) indications to percutaneous

revascularization, based on clinical criteria (hemodynamic instability, ongoing or relapsing

myocardial ischemia) and one of the following angiographic features: TIMI flow < 3, proximal

coronary location, coronary narrowing > 70% in diameter according to visual estimation. Exclusion

criteria were: 1) iatrogenic coronary artery dissection; 2) coronary artery dissection in the context of

atherosclerotic plaque; 3) contraindication to BVS implantation, including vessel diameter > 4.0

mm, bifurcation lesion with large (> 2.5 mm) side branch and intended two-stent strategy; 4)

contraindication to dual anti-platelet therapy. In this prospective study, SCAD patients were

included with both prospective and retrospective methods. In particular, 5 patients were

retrospectively enrolled because of their complete adequacy with prospectively established

inclusion and exclusion criteria. REDCap© web application was used to collect epidemiological,

clinical, angiographic and outcome data. Cardiovascular risk factors, medications on presentation,

clinical and hemodynamic status were collected. Indeed, SCAD risk factors and associate

conditions, including fibromuscular dysplasia, estro-progestinic drugs, peri-partum status,

connective tissue disorders and systemic inflammation diseases were investigated. Furthermore,

trigger events according to those identified by previously published studies, such as emotional

stress and/or strenuous physical effort, were registered.

Percutaneous Coronary Intervention.

Coronary intervention was performed by radial approach, or femoral approach when radial was

judged not suitable for catheterization. Diagnosis of SCAD was based on angiography when

pathognomonic angiographic appearance with contrast dye staining of the arterial wall with

multiple radiolucent lumens was appreciated (type I of Saw Classification) (27); smooth and diffuse

narrowing with abrupt change in arterial caliber, with demarcation from normal diameter to diffuse

narrowing, or long and linear stenosis, or hazy long lesions (type II and III of Saw classification)

were considered as SCAD, especially in absence of atherosclerotic changes in the other vessels and

high clinical suspicion of SCAD (27); when angiography was considered inconclusive diagnosis

was definitely accomplished by IVUS (28, 29). At intracoronary tomographic imaging the evidence

of double lumen with intimo-medial membrane identification in the context of culprit lesion was

considered diagnostic; additional, but not mandatory, findings included presence of one or more

intimal rupture site, thrombi formation in the false lumen (hematoma), intimal flaps (6, 8, 30).

Angiographic imaging characteristics were recorded, including culprit vessel and lesion location,

presence of intimal tear and intramural hematoma (type of SCAD), lesion length, TIMI flow grade,

and multivessel involvement. Direct deployment of scaffold was suggested but not mandatory. Full-

coverage of lesion represented the indented strategy. In bifurcation lesions one scaffold strategy

was strongly recommended, with mini-kissing balloon allowed in case of suboptimal side branch

result, and bailout hybrid strategy with metallic platform left to operator judgment.

Outcome.

Primary endpoints were device success, angiographic success and procedural success. Device

success (lesion level) was defined as successful delivery and deployment of the scaffold at the

intended target lesion and successful withdrawal of the delivery system with attainment of final in-

scaffold residual stenosis of less than 30% by quantitative coronary angiography (QCA) or by

visual estimation if QCA unavailable. Angiographic success was defined as TIMI-3 flow and

residual stenosis <30% at the end of procedure, regardless of device success (24). When bailout

device was used, the success or failure of the bailout device was a criterion for angiographic success but not for device success. Clinical procedural success (patient level) was defined as angiographic success without the occurrence of cardiac death, myocardial infarction (re-infarction in case of STEMI/NSTEMI) or TVR during the hospital stay and anyway up to 7 days after the procedure (31). All cases of death, cardiovascular death, non-fatal myocardial infarction and TVR, occurring during hospital stay and follow-up were recorded as adverse events. Clinical status was evaluated at 6 and 12-month follow-up; either coronary angiography or ECG-gated coronary CT scan were performed, according to hospital policy, at 12-month follow up, unless contraindicated.

Statistical analysis

Continuous data were summarized with mean ± standard deviation when normally distributed, with median and interquartile range (IQR) in case of non-normal distribution. Categorical data were expressed as numbers and percentages. Follow-up data were considered complete in case of patient survival to adverse events or at the end of overall follow-up. SPSS version 21 (SPSS Chicago, Ill, USA) was used for statistical analysis.

Results

The study enrolled 27 SCAD patients at 12 Italian Hospitals. Mean age of population was 48.0± 8.6

years (range 33-71), 92.6% were women with low rates of atherosclerotic risk factors, as expected

(Table 1). STEMI was the clinical presentation in 48.1 %, NSTEMI/UA in 37.0% and life-

threatening arrhythmias (VT/VF) in 14.8% of patients (Figure 1). Specific SCAD risk factors and

trigger events are shown in Table 1. Multivessel involvement was observed in 5 (18.5%) patients, in

2 cases requiring multivessel intervention. Thus the study included 29 lesions in 27 patients. Vessel

distribution and angiographic pattern of SCAD is illustrated in Table 2 and Figure 1. Baseline

angiography showed TIMI-0/1 flow in 31.0% of cases, TIMI-2 flow in 27.6% and TIMI-3 flow in

41.4% respectively. IVUS was used in 44.8% of lesions. Mean BVS total length was 57.4 ± 28 mm

and 93.1% of lesions were longer than 20 mm (Table 2). In 79.3% of cases 2 or more scaffold were

implanted. When an overlap between scaffolds was needed, the most used technique was marker-to-

marker (54.5%), and in 87.0% of vessels a distal-to-proximal deployment technique was adopted

(Table 3). Post dilatation was applied in 72.4% of cases, and in 5 vessels (17.2%) a bifurcation

treatment was undertaken (Table 2), in one case with two-stent approach (T-stent using DES on

side branch). Device success was obtained in 100% of cases. Angiographic success was 96.6%

(28/29 vessels): post-procedural TIMI-3 flow was observed in 96.6% of vessels, with a single case

of TIMI 2 flow after scaffold deployment despite the achievement of device success; no cases of

residual stenosis were observed. Procedural success was achieved in 25 of 27 patients (92.6%): in

one case angiographic success was not achieved, in the other one despite angiographic success TVR

was performed during hospitalization, due to symptomatic SCAD progression at scaffold distal

edge; a DES was successfully deployed distally to the scaffolds. No cases of death or myocardial

infarction were registered during hospital stay neither at follow-up. TVR at follow-up occurred in

one case (3.7%) because of a non-symptomatic BVS recoil at the planned follow up coronary

angiography. Coronary imaging (either invasive or not invasive) follow-up was performed in 15

patients with 1 year follow up showing BVS patency in 14 of 15 cases; one case of recurrent SCAD

and one case of SCAD persistence were registered.

Table 1. Baseline Characteristics and Hospital Presentation of SCAD Patients (n=27)

Female sex	25 (92.6%)
Mean age (years)	48.0 ± 8.6
Hypertension	8 (29.6%)
Cigarette smoke	7 (25.9%)
Dyslipidemia	4 (14.8%)
Diabetes mellitus	0
Family history of CAD	4 (14.8%)
Estro-progestinic drugs	3 (12.0% among women)
Benzodiazepine drugs	2 (7.4%)
Antidepressant drugs	2 (7.4%)
Pregnancy/puerperium	0
Collagen disease	0
Strenuous effort	3 (11.1%)
Emotional stress	6 (22.2%)
Coagulation abnormalities	0
Thyroid dysfunction	5 (18.5%)
Clinical presentation	
STEMI	13 (48.2%)
NSTEMI/UA	10 (37.0%)
VT/VF	4 (14.8%)
Killip Class at presentation	
1	25 (92.6%)
2	2 (7.4%)
3 or 4	0

Values are n (%) or mean ± SD.

CAD = coronary artery disease; NSTEMI/UA = non ST-elevation myocardial infarction/unstable angina; SCAD = spontaneous coronary artery dissection; STEMI = ST-elevation myocardial infarction; VT/VF = ventricular tachycardia/ventricular fibrillation.

Table 2. **Coronary Artery Angiographic Findings in SCAD vessels (N = 29)**

Multivessel involvement	5 (18.5%)
Culprit coronary arteries	
LMCA	0
LAD	20 (69%)
LCx	4 (13.8%)
RCA	5 (17.2%)
Presence of intimal tear	17 (58.6%)
Flow-limiting lesions (TIMI flow 0 or 1)	9 (31.0%)
Lesion lenght >20mm	27 (93.1%)

Values are n (%).

LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

Table 3. Procedural Characteristics (N = 29)

IVUS guiding	13 (44.8%)
Pre-dilatation	13 (44.8%)
>1 scaffold needed	23 (79.3%)
Mean total scaffold lenght	57.4 ± 28.0
BVS Overlap technique*	
marker-to-marker	18 (54.5%)
marker-over-marker	6 (18.2%)
marker-inside-marker	1 (3.0%)
scaffold-to-scaffold	6 (18.2%)
minimal gap	1 (3.0%)
Distal-to-proximal overlap	20/23 (87.0%)
Post-dilatation	21 (72.4%)
Bifurcation treatment	5 (17.2%)
Side branch treatment technique	
Provisional	3/5 (60%)
Kissing	1/5 (20%)
2-stent technique	1/5 (20%)
Hybrid procedure	5 (17.2%)
DES-BVS relative position	
other vessel	1/5 (20%)
distal	1/5 (20%)
proximal	2/5 (40%)

in scaffold (bail-out)	0/5
side branch	1/5 (20%)
Device success	29 (100%)
Residual stenosis <30%	29 (100%)
Full coverage	26 (89.7%)
TIMI flow 2 or 3 (%)	29 (100%)
Angiographic success	28 (96.6%)
Dissection extension	3 (10.3%)
Procedural success	25/27 (92.6%)
ST resolution >70% (%)	13/16 (81.3%)
In hospital events	
Death	0
Non-fatal MI	0
Angina relapse	4 (14.8%)
TVR	1 (3.7%)

Values are n (%) or mean ± SD. *Data available for 32 of 41 overlap.

BVS = bioresorbable vascular scaffold; DES = drug eluting stent; IVUS = intravascular ultrasound;

MI = myocardial infarction; TVR = target vessel revascularization.

Table 4. Follow-up

Clinical follow up	6 months NO. OF PATIENTS (overall = 26)	12 months NO. OF PATIENTS (overall = 26)
Death	0	0
Cardiovascular death	0	0
Non-fatal MI	0	0
TVR	0	1 (3,8%)

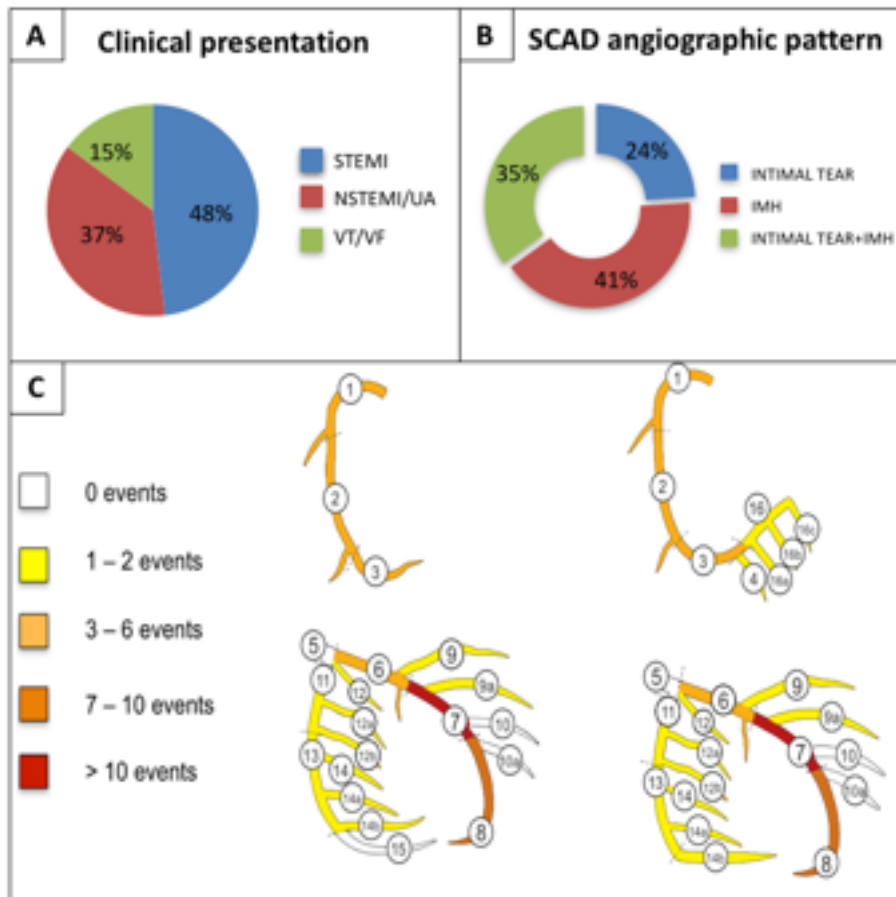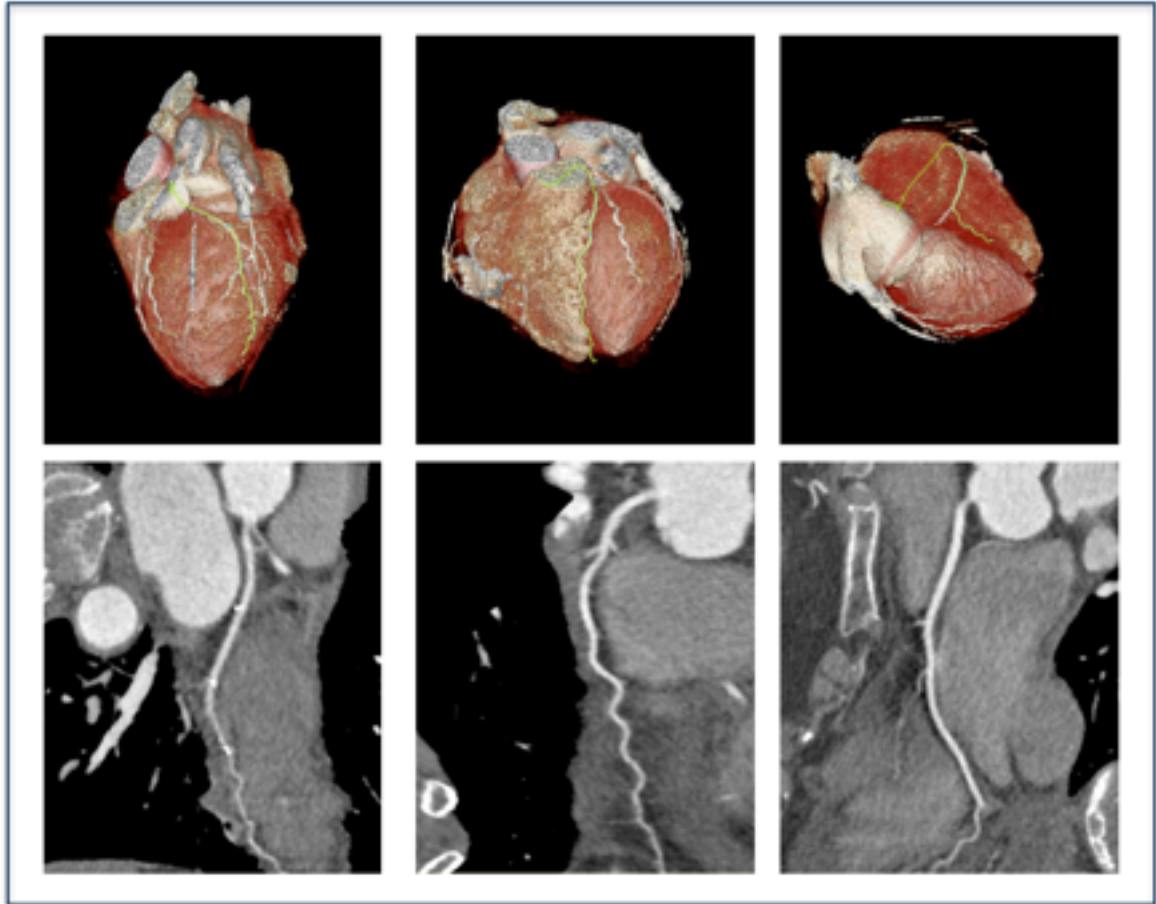| Angio/CT scan follow up – 12 months	NO. OF PATIENTS (%) (overall = 15)
BVS patency	14 (93.3%)
Haematoma/dissection persistence	1 (6.7%)
Haematoma/dissection recurrence	1 (6.7%)
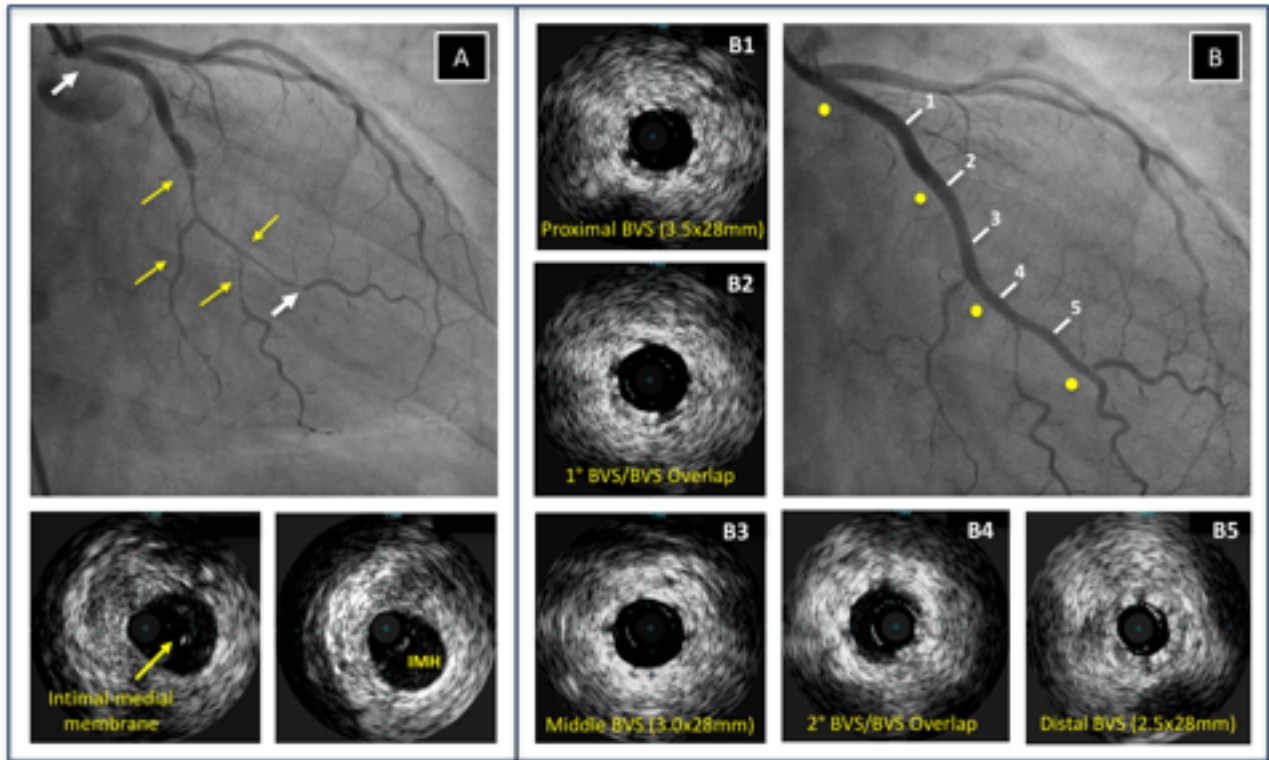
Figure 1

Figure 2

Figure 3

Discussion

Since the earliest report (105), growing interest has been raised for BVS utilization in SCAD patients, together with intravascular imaging (106), which is now advocated as the ideal strategy (107). Nevertheless, data about the efficacy and safety are still limited to case reports or small studies (108, 109). To address this issue we evaluated the wider (to the best of our knowledge) cohort of patients treated in this way.

To assess feasibility, records regarding device and angiographic success were analyzed. As previously assessed, the choice between medical conservative management and percutaneous coronary intervention was based on clinical conditions and angiographic findings, with PCI performed on patients with hemodynamic instability, ongoing and/or relapsing ischemia and compromised angiographic pattern.

Despite the technical difficulties linked to this setting, with high risk of failure and peri- or post procedural complications, data about BVS delivery and deployment were encouraging, also considering the complexity of treated coronary lesions: 93.1% of SCAD lesions were longer than 20.0 mm and mean scaffold length was 57.4 ± 28 mm (range: 12 to 130 mm). Furthermore, multivessel disease was found in 5 of 27 patients (18.5%), and two of them underwent PCI with

BVS deployment also on the second vessel. Device success was achieved in 100% of cases, i.e. in 29 of 29 treated lesions. The operator was able to reach or pass through the target lesion in the totality of cases and all BVS were implanted on planned site even if a predilatation technique was infrequently performed. In fact predilatation can help BVS passage and deployment but, in the contest of SCAD, could worsen coronary dissection with iatrogenic extension of lesion. Therefore, despite BVS difficult management compared to metallic DES, caused by a more challenging device navigability and by struts bigger dimensions (157µm for Absorb vs 81µm for Xience V), scaffolds deployment in SCAD proved to be achievable and effective even when pre dilatation was not performed.

Angiographic success was achieved in 96.6% of cases. Every treated lesion showed final in-scaffold residual stenosis less than 30% by quantitative coronary angiography (QCA) and 96.6% of target vessels achieved an optimal post procedural TIMI flow. In only one target vessel blood flow improvement was not achieved, being both pre and post procedural TIMI flow rate 2: albeit IVUS evaluation demonstrated an incomplete lesion coverage, no adverse events were registered.

As regards safety, procedural success (patient level) was achieved in 92.6% of treated patients. In particular, one of two cases of procedural failure was due to the lack of angiographic success, without the development of any adverse event during hospital stay; the other one, instead, was due

to a TVR, performed for subsequent ischemia a few days after BVS deployment. At coronary

angiography there was no evidence of scaffold recoil or thrombosis, but SCAD progression at

scaffold distal edge was noticed. A DES was deployed distally to previous scaffold, and patient

experienced no other complications or adverse events afterwards.

Safety can be confirmed by follow up findings. Clinical follow up involved 26 patients at 12

months endpoint (only one patient, who moved to a foreign country, was lost at follow up). After

hospital discharge, a single adverse event was reported: 12 months after BVS deployment, a 33-

year-old woman underwent TVR: indeed, planned follow up coronary angiography of a non

symptomatic patient showed a late BVS recoil affecting one of the two devices deployed in RCA

mid-distal segment; a DES was therefore deployed inside the scaffold. In the present study,

differently from other BVS studies, involving patients with atherosclerotic coronary artery disease,

no cases of scaffold early and late thrombosis were observed. Making a comparison between our

prospective multicenter registry and a meta-analysis published by Cassese et al. in 2016 (110), an

important difference regarding scaffold thrombosis can be highlighted: the population described by

Cassese is composed by patients with atherosclerotic coronary disease, randomized for receiving

DES versus BVS during revascularization and evaluated at 12 months follow up. Adverse events

(target vessel revascularization, target lesion failure, myocardial infarction and death) were similar

in the two randomized groups, although BVS patients developed a higher scaffold thrombosis risk

(in particular between the first and the 30th day since scaffold deployment) compared to the DES

group (110). In a study from Puricel et al. the incidence of probable and definite scaffold

thrombosis was 1.8% at 30 days and 3.0% at 12 months, but when a BVS-specific implantation

strategy was applied, 12 months scaffold thrombosis rate fell to 1.0% (111). In fact, the higher risk

of scaffold thrombosis can be overcome by the operator who is in charge to ensure optimal

implantation (112). Despite the exiguity of our population and the need for further studies with a

larger sample and a longer follow up, BVS deployment in the contest of SCAD seems to be related

to a smaller scaffold thrombosis risk compared to the same procedure performed in the contest of

atherosclerotic coronary disease. Since early thrombosis is likely to be linked to deployment

technique and most cases are explainable with the onset of procedural problems (such as incomplete

stent apposition or incomplete stent expansion), BVS deployment seems to be more feasible on

smooth and non-calcified lesions (as happens in SCAD) rather than atherosclerotic plaques,

especially when irregular and rich in calcium (113). Thanks to SCAD characteristics, BVS was able

to fit optimally to vessel wall, even if a non aggressive deployment protocol was applied: in our

study both pre and post dilatation were performed in a variable percentage of patients, according to

operator choice, and a high device success rate was registered, with all cases of final in-scaffold

residual stenosis less than 30%. Furthermore, after BVS deployment intra-coronary imaging could

play an important role identifying scaffold expansion and/or apposition irregularities, and thus

allowing the operator to perform a further post dilatation with the aim of reducing early thrombosis

risk, that is often related to malapposition (111). The larger use of intracoronary imaging may

reduce other procedural complications related to stent deployment, such as SCAD extension: in our

study, mainly thanks to IVUS guiding, iatrogenic SCAD extension rate was low and no serious

complications like Left Main iatrogenic involvement or extension-related blood flow impairment,

previously described (107, 114-116), were reported. Another issue we can address is the

comparison between revascularization and conservative management of SCAD: most authors agree

that while the first choice is conservative management, the strategy should be tailored to the clinical

and angiographic setting, with revascularization indicated in proximal segments, flow-limiting, or

ischemia-driving lesions. In fact, all the patients we enrolled were deemed to need an invasive

management. Nevertheless, outcome of conservative management is not always favourable, with a

significant number of patients with angina relapse (19.4% in hospital, in Alfonso et al, 2012 (117))

or in-hospital myocardial re-infarction (4.5% in Saw et al, 2014 (118)): our study is on a small

sample size, but with 14.8% and 0% of in-hospital angina relapse and in-hospital myocardial re-

infarction, respectively, data are encouraging.

As regards imaging techniques at follow up evaluation, a coronary angiography or a ECG-gated coronary computed tomography (according to hospital policy and operator choice) was performed 12 months after SCAD event in 15 patients, evaluating 16 of 29 coronary arteries (55.2%). In 15 (93.8%) of evaluated vessels, BVS patency was attested, with no evidence of late thrombosis or restenosis; in one case a non symptomatic late BVS recoil was observed, as aforementioned. One case of recurrent SCAD and one case of SCAD persistence were registered too; the first one with SCAD pathognomonic angiographic appearance affecting a not previously involved vessel, the second one was due to extra-scaffold intramural hematoma persistence without BVS patency impairment. Follow up results confirm not only procedural success but also the efficacy of BVS apposition in SCAD lesions. Besides the absence of scaffold thrombosis, we registered a very low TVR rate: restenosis, indeed, may be related to coronary lesions characteristics, with a lower TVR risk in SCAD patients due to the lack of atherosclerotic disease in epicardial vessels.

Conclusions

Revascularization through BVS deployment is increasingly advocated as the ideal strategy in the setting of flow-limiting SCAD. Our study, on the largest cohort of patients to date, suggests the feasibility and safety of this technology, with high rates of angiographic and procedural success, and favorable 1-year results. Nevertheless, longer evaluation in larger studies is needed.

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