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CARDIOVASCULAR DISEASE AND STROKE (P PERRONE-FILARDI AND S. AGEWALL, SECTION EDITORS)

Stable Angina Pectoris

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Abstract The stable coronary artery disease (SCAD) population is a heterogeneous group of patients both for clinical presentations and for different underlying mechanisms. The recent European Society of Cardiology guidelines extensively review SCAD from its definition to patients' diagnostic and therapeutic management. In this review, we deal with five topics that, in our opinion, represent the most intriguing, novel and/or clinically relevant aspects of this complex coronary condition. Firstly, we deal with a peculiar SCAD population: patients with angina and 'normal' coronary arteries. Secondly, we reinforce the clinical importance of a diagnostic approach based on the pretest probability of disease. Thirdly, we review and critically discuss the novel pharmacological therapies for SCAD patients. Finally, we analyse the results of the most recent clinical trials comparing revascularization versus optimal medical therapy in SCAD patients and review the currently recommended use of intracoronary functional evaluation of stenosis.

Keywords Stable coronary artery disease · Microvascular angina · Vasospastic angina · Pretest probability of the disease · Optical medical therapy · Fractional flow reserve

Introduction

The recent European Society of Cardiology (ESC) guidelines [1••] provide a comprehensive and updated overview of contemporary management in patients with known or suspected stable coronary artery disease (SCAD).

The SCAD population is extremely heterogeneous, including:

1. Patients symptomatic for stable angina pectoris or angina equivalent (e.g. dyspnoea)
2. Patients with a history of obstructive or non-obstructive coronary artery disease (CAD), who have become asymptomatic with treatment and need regular follow-up
3. Patients reporting symptoms for the first time, but already in a chronic stable condition (e.g. symptoms presents for several months)

Therefore, different phases of CAD are included in SCAD, with the exception of acute coronary syndromes (ACS). Narrowings of 50 % or more in the left main coronary artery and 70 % or more in one or several of the major coronary arteries have traditionally represented the pathophysiological mechanism underlying SCAD, causing exercise- and stress-related chest symptoms.

Actually, SCAD is more complex than this. In fact, the wide spectrum of SCAD clinical presentations is due to different underlying mechanisms:

1. Plaque-related obstruction of epicardial arteries
2. Focal or diffuse spasm of normal or plaque-diseased arteries
3. Microvascular dysfunction
4. Left ventricular dysfunction caused by prior acute myocardial necrosis and/or hibernation (ischaemic cardiomyopathy)

For all these reasons, it is difficult to assess the real prevalence and incidence of SCAD, because its definition differs among different studies. The prognosis of SCAD patients can be derived from clinical trials of anti-anginal and preventive

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therapy and/or revascularization. An important bias of these data is the selected nature of the populations studied. However, estimates of annual mortality rates range from 1.2 to 2.4 % [2–5], with an annual incidence of cardiac death between 0.6 and 1.4 %.

In this review, we focus on five 'hot topics' regarding SCAD, which represent, in our opinion, the key messages from the recent ESC guidelines:

1. SCAD not related to fixed macrovascular obstruction
2. The importance of assessing the pretest probability (PTP) of the disease
3. Some novel pharmacological therapies
4. Revascularization versus optimal medical therapy (OMT) on the basis of the results of recent trials
5. The importance of functional assessment of discrete coronary lesions and/or myocardial ischemia in proceeding to optimal coronary revascularization.

Microvascular Dysfunction and Coronary Vasospasm: Angina with 'Normal' Coronary Arteries

Patients, especially women, with symptoms of chest pain or shortness of breath on exertion without significant obstructive CAD on invasive coronary angiography (ICA) have represented an unsolved conundrum for cardiologists for decades [6, 7].

Patients of this kind can experience different types of chest pain, which are associated with different diseases:

1. Typical angina (sometimes with prolonged duration or inconsistent relationship to exercise), which is often associated with abnormal results of stress tests. This type of angina can be related to microvascular disease (microvascular angina). These patients usually present with typical atherosclerotic risk factors and, for this reason, frequently undergo a variety of non-invasive stress tests, and even repeated ICA, with the intention of revascularization.
2. Typical angina, in terms of location and duration, but occurring predominantly at rest (atypical angina), due to coronary spasm (vasospastic angina). This kind of presentation may also lead to emergency coronary angiograms being performed.

Arterial hypertension, either with or without associated ventricular hypertrophy, is frequently encountered in the population with chest pain and 'normal coronary arteries'.

Even in the ACS setting, myocardial infarction (MI) with angiographically normal coronary arteries (MINCA) is an important subtype of MI. A recent study prospectively included MINCA patients who underwent cardiovascular magnetic resonance imaging in five different coronary care units in the Stockholm metropolitan area [8]. The incidence of MINCA was commoner than previously reported. A particularly intriguing aspect was that two thirds of the cardiovascular magnetic resonance images appeared completely normal, confirming the increasing importance of this new nosographic entity, and the need for further exploration of the underlying physiopathological mechanisms.

Microvascular Angina

Primary coronary microvascular disease is an exclusion diagnosis in patients with sufficiently typical chest pain in whom, despite clinical and functional objective signs of myocardial exercise-induced ischaemia as evidenced by myocardial perfusion imaging, coronary angiography fails to show fixed or dynamic obstructions in epicardial coronary arteries [9]. Specific diseases can also result in microvascular disease [10], such as hypertrophic cardiomyopathy or aortic stenosis (secondary coronary microvascular disease).

In patients with coronary microvascular disease, intracoronary injection of acetylcholine may cause diffuse coronary artery spasm, pronounced in the distal epicardial coronary arteries and extending to microvasculature [11].

Vasospastic Angina

In vasospastic coronary disease, angina occurs typically at rest. Pain episodes are more frequent at night and in the early morning hours. Nitrates usually relieve the pain within minutes.

The ECG during vasospasm usually shows ST elevation. On ICA, these patients may present with focal occlusive spasm (Prinzmetal's angina or variant angina) [12]. However, most patients with coronary vasospasm show distally pronounced diffuse subtotal vasospasm, associated with ST depression. On the other hand, spontaneous spasm during coronary arteriography is only occasionally observed in patients with symptoms suggestive of vasospastic angina.

Therefore, provocation tests are commonly used to demonstrate the presence and also the type of coronary vasospasm. The most used methods are acetylcholine or ergonovine injections into the coronary artery. Incremental intracoronary doses are used for both: up to 200 μg for acetylcholine, and up to 60 μg for ergonovine, separated by intervals [13].

Acetylcholine or ergonovine provocation tests are safe [14, 15]. It is of paramount importance that ergonovine is infused selectively into the left coronary artery or the right coronary artery, as fatal complications may occur with intravenous injection, because of prolonged spasm involving multiple vessels [16].

The Importance of Assessing the PTP of the Disease

The ESC guidelines [1••] suggest a three-step approach in decision-making in patients with suspected SCAD. Step 1 of this process is the determination of the PTP. Step 2 is represented by non-invasive tests to diagnose SCAD. Step 3 is the institution of OMT and the risk stratification of future events.

SCAD diagnosis frequently relies on non-invasive cardiac tests, the interpretation of which requires a Bayesian approach. The two key players in this approach are clinicians' pretest estimates of disease (the so-called pretest probability, PTP), and the results of diagnostic tests. Their combination generates individualized posttest disease probabilities for a given patient.

PTP is deeply influenced by the prevalence of the disease in the population studied, the clinical presentation and the characteristics of an individual patient, including age, gender and the features of the symptoms. Although this approach has been recommended for a long time, its widespread application is still suboptimal. If properly applied, the PTP versus post-test probability concept may dramatically help patients and physicians to streamline the diagnostic and therapeutic approach to this patient population.

Traditionally, the accuracy of a given diagnostic method is given by its sensitivity and specificity, but this information is not always suitable to describe how a test performs in the clinical setting.

First, the diagnostic test performance may vary from one patient to another. Moreover, although there is no mathematical correlation between sensitivity, specificity, and PTP, the correlation between them is often shown in clinical practice. For example, it is well known that many tests perform better in low-risk populations (e.g. coronary computed tomography angiography) than in other settings. Therefore, the selection of diagnostic testing needs to take into account the PTP, because of the above-mentioned connection between PTP and the performance of diagnostic methods. A test is harmful when the number of errors (false test results) is higher than the number of diagnosis/disease rule-outs (correct test results).

In the diagnosis of CAD, contemporary tests have sensitivities and specificities of approximately 85 %. Therefore, 15 % of patients will have a false test result and, as a consequence, performing no test at all will provide fewer incorrect diagnoses in patients with a PTP below 15 % (assuming all patients to be healthy) or a PTP above 85 % (assuming all patients to be diseased).

Hence, the ESC guidelines [1••] recommend no testing in patients with

1. PTP below 15 %
2. PTP above 85 %

In the first case, the underlying assumption is that the patients have no obstructive CAD, whereas in the second case, the question would be how to handle CAD in this specific individual more than how to diagnose it.

For the same reason, despite its high specificity (about 90 %), exercise test ECG is not indicated as a diagnostic test in patients with PTP above 65 %, because of its low sensitivity (only 50 %) [17]. In fact, in patients of this kind, the number of false test results will be higher than the number of correct test results.

On the other hand, thanks to its high negative predictive value, coronary computed tomography angiography may be considered as an alternative to ischaemia testing, especially in patients with chest pain symptoms with intermediate PTPs lower than 50 % [18].

Another example in which PTP affects clinical decision-making is in patients with a reduced left ventricular ejection fraction of less than 50 % and typical angina. Their PTP is extremely high; therefore, they should be offered ICA without previous testing.

Figure 1 summarizes the sensitivity and specificity of contemporary SCAD non-invasive diagnostic tests, and Figs. 2 and 3 summarize the diagnostic management in patients with suspected SCAD and the indication for non-invasive testing depending on the PTP.

Beyond diagnosis, a critical step to consider in managing SCAD patients is prognostic assessment. Establishing prognosis during diagnosis is crucial for two main reasons. The former is the identification of patients with severer forms of disease, who may have a better outcome with more aggressive investigation and subsequent intervention. The latter is the identification of those patients with a less severe form of disease and a good prognosis, thereby avoiding unnecessary invasive and non-invasive tests and revascularization procedures.

Beyond conventional risk factors for the development of CAD [19], other important prognostic indicators to assess in SCAD patients are

1. Left ventricular ejection fraction
2. Signs and symptoms of heart failure
3. Number of diseased vessels
4. Location and severity of the disease
5. Burden of ischaemia
6. Functional capacity
7. Heart rate [20]
8. Presence of depression

In everyday clinical practice, diagnostic and prognostic assessments must go hand in hand, as diagnostic tests almost always offer prognostic information.

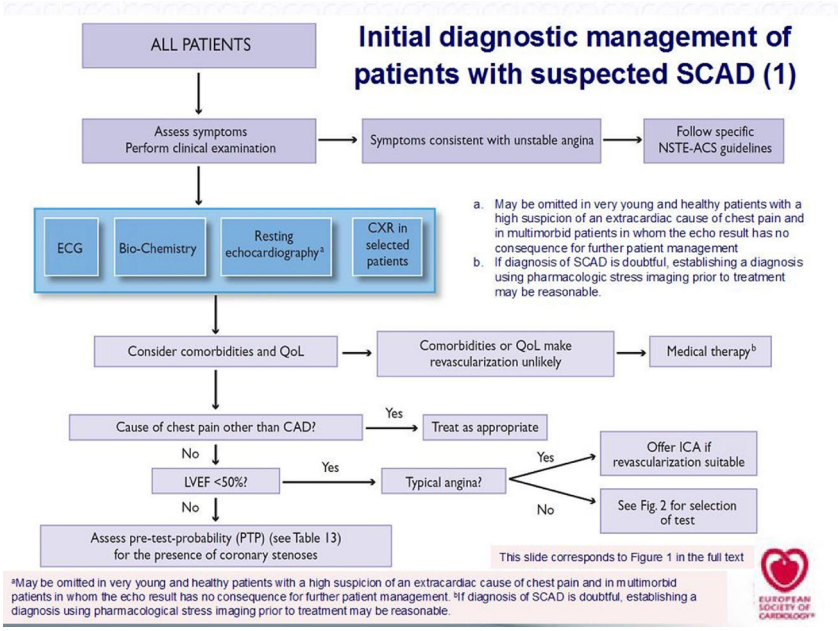

Fig. 1 Characteristics of tests commonly used to diagnose the presence of coronary artery disease (*CAD*). (Reprinted with permission from Montalescot et al. [1••])

Novel Pharmacological Targets for SCAD: Heart Rate and Late Sodium Currents

Before we consider new pharmacological therapies for patients with SCAD, it is important to restate that the most effective of all preventive measures is not a drug but a quit. The benefits of smoking cessation have been extensively reported [21], and quitting smoking is associated with a reduction in mortality of 36 % after MI [22].

Relief of symptoms and prevention of cardiovascular events are the Scylla and Charybdis of the pharmacological management of SCAD. Immediate treatment or prevention of angina is given by rapidly acting formulations of nitroglycerin, since they are able to provide immediate relief of the angina symptoms once the episode has started or when it is likely to occur.

Anti-ischaemic drugs, lifestyle changes, regular exercise training, patient education and revascularization result in long-term prevention of symptoms. Reduction of the incidence of acute thrombotic events and of ventricular dysfunction development is the core of MI and death prevention in SCAD patients. These aims are achieved by reducing plaque

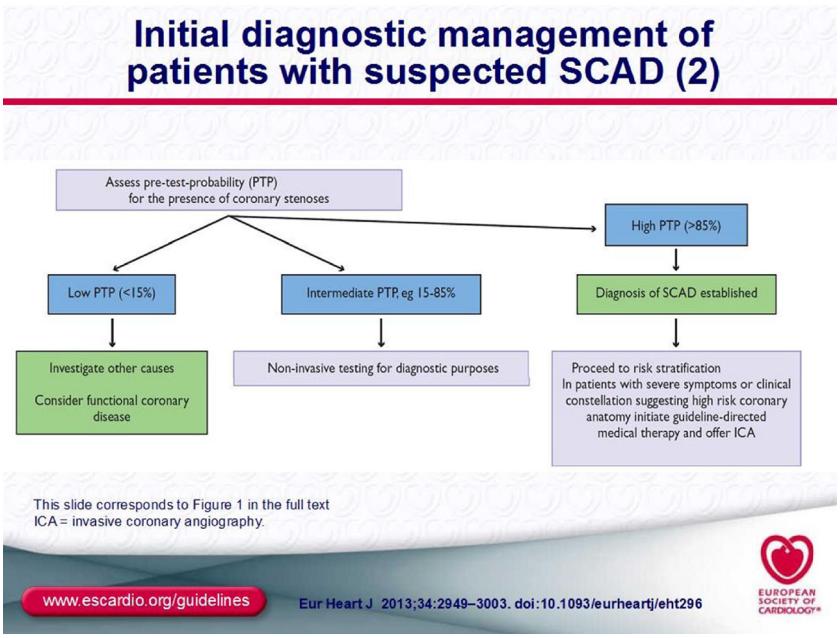

Fig. 2 Initial diagnostic management of patients with suspected stable CAD (*SCAD*): 1. *CXR* chest X-ray, *ICA* invasive coronary angiograph, *LVEF* left ventricular ejection fraction, *NSTE-ACS* non-ST-elevation acute coronary syndrome, *QoL* quality of life. (Reprinted with permission from Montalescot et al. [1••])

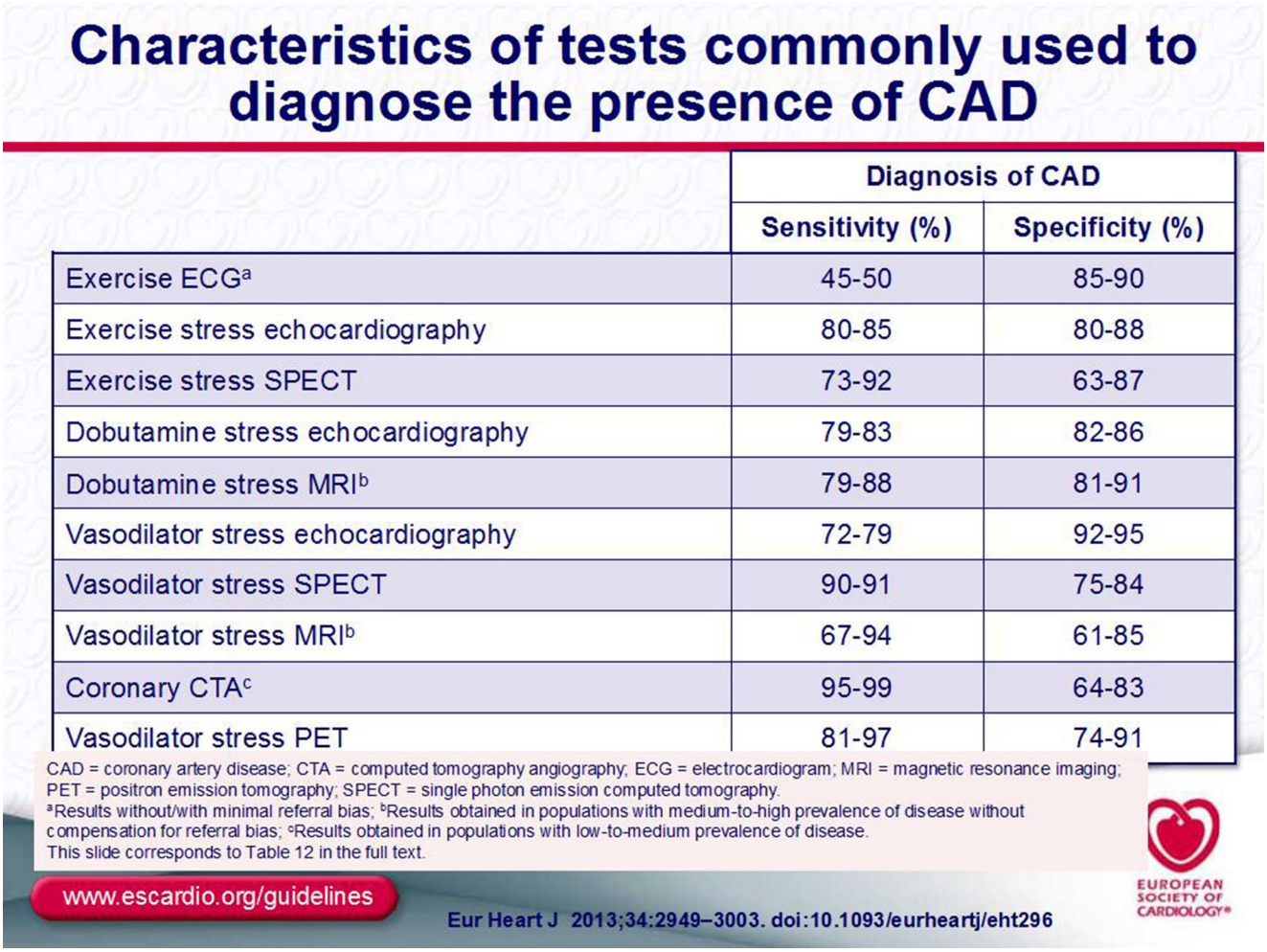

Fig. 3 Initial diagnostic management of patients with suspected SCAD: 2. (Reprinted with permission from Montalescot et al. [1••])

progression, and stabilizing plaque, by reducing inflammation and preventing thrombosis, should plaque rupture or erosion occur. In the ESC guidelines [1••], the strongest level of evidence (class I, level of evidence A) indicates as first-line treatment for SCAD patients, ß-blockers and/or calcium channel blockers to control heart rate and symptoms [23, 24], whereas low-dose aspirin [25, 26] and statins [27] for event prevention are also to be implemented immediately.

Short-acting nitrates are recommended in class I (level of evidence B) to control symptoms [24–28].

The more recent pharmacological therapies, including ivabradine, nicorandil and ranolazine, are indicated as second-line treatment (class IIa, level of evidence B) [23, 29–37].

Ivabradine

Ivabradine is a specific inhibitor of the I_f current in the sinoatrial node. As a result, it is a pure heart-rate-lowering agent in patients with sinus rhythm as it acts primarily on sinus node cells and not on other heart cells. Ivabradine does not affect blood pressure, myocardial contractility, intracardiac conduction or ventricular repolarization, thereby decreasing the myocardial oxygen demand without an effect on inotropism or blood pressure [38–40].

Treatment with ivabradine therefore provides an opportunity to assess the effects of lowering the heart rate without directly altering other aspects of cardiac function. Ivabradine has been proven to effectively prevent myocardial ischaemia and treat symptoms in patients with chronic stable angina pectoris [41].

Ivabradine was non-inferior to atenolol or amlodipine in patients with SCAD; the addition of treatment with ivabradine, 7.5 mg twice daily, in patients already treated with atenolol gave better control of heart rate and anginal symptoms [30, 33]. In 1,507 patients with prior angina enrolled in the Morbidity–Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease and Left Ventricular Dysfunction (BEAUTIFUL) trial, ivabradine reduced the composite primary end point of cardiovascular

death, hospitalization for MI and hospitalization for heart failure, and reduced hospitalization for MI. The effect was greater in patients with a heart rate of 70 bpm or greater [37]. Ivabradine is thus an effective antianginal agent, alone or in combination with ß-blockers.

Ivabradine was approved by the European Medicines Agency for treatment of chronic stable angina in patients intolerant to, or inadequately controlled by, ß-blockers and whose heart rate exceeded 60 bpm (in sinus rhythm) [30].

Ranolazine

The mechanism of action of ranolazine is selective inhibition of the late inward sodium current with anti-ischaemic and metabolic properties (reducing calcium overload and thereby left ventricular diastolic tension) [42, 43]. Therapeutic dosages ranges from 500 to 2,000 mg daily. Its primary effect is angina occurrence reduction and increase in exercise capacity. These effects are achieved without changes in heart rate or blood pressure [43]. The European Medicines Agency approved ranolazine in 2009 for 'on-top' treatment in stable angina in patients inadequately controlled by (or intolerant to) ß-blockers and/or calcium antagonists [44].

Ranolazine has been tested in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation Acute Coronary Syndromes: Thrombolysis in Myocardial Infarction (MERLIN TIMI 36) trial [35], in which 6,560 patients presenting with recent non-ST-elevation ACS were enrolled. In this trial, ranolazine therapy showed no overall benefit. Ranolazine reduced recurrent ischaemia in patients with prior chronic angina (HR: 0.78; 95% CI: 0.67 to 0.91; $p = 0.002$). An intriguing result was in that ranolazine reduced the incidence of newly increased haemoglobin A_{1c} (HbA_{1c}) levels by 32 % after the infarction [35, 36].

This possible link between ranolazine and diabetes was analysed in the recent Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) study [45]. In this trial, ranolazine significantly reduced angina frequency and sublingual nitroglycerin use in 949 diabetes patients already receiving one or two antianginal drugs and led to less use of sublingually administered nitroglycerin. These results suggest that this drug can be added on top of first-line antianginal therapy, in particular in patients with higher HbA_{1c} levels. Ranolazine is a weak inhibitor of cytochrome P450 3A; therefore, plasma levels of other cytochrome P450 3A inhibitors (i.e. diltiazem, verapamil, macrolide antibiotics, grapefruit juice) are increased. Clearance of ranolazine is reduced by renal insufficiency and hepatic impairment [42]. Ranolazine increases corrected QT, and should therefore be used carefully in patients with QT prolongation or who are receiving QT-prolonging drugs [42].

Reshaping ICA Benefits: SCAD Management Turns Back Time?

In the recent ESC guidelines [1••] the need for event risk stratification in SCAD patients is particularly stressed, since the prognostic benefit of revascularization is strongly reshaped. Therefore, selection of patients who can have prognostic benefit from revascularization is of paramount importance. This stratification is made according to all-cause death risk, as it is the most clear and reproducible end point throughout all clinical trials.

High-risk patients (who will therefore need revascularization) are identified through an annual mortality risk of more than 3 %. In the previous ESC guidelines, the threshold was lower (more than 2 % annual mortality) [17].

The risk of events is assessed by clinical evaluation, ventricular function, response to stress testing and coronary anatomy.

The debate about prognostic benefit of revascularization versus OMT in SCAD patients climaxed after the publication of the results of the three most recent studies that investigated that topic: Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) [46], Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) [2] and Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2 (FAME 2) [47••]. These trials are the largest and most informative studies for this comparison, and are briefly summarized in the following sections.

COURAGE Trial

The COURAGE trial (n=2,287), published in 2007, compared percutaneous coronary intervention (PCI) plus OMT with OMT alone in patients with SCAD or ischaemia and coronary lesions suitable for PCI [46].

The COURAGE trial patients' enrolment characteristics were as follows:

- Canadian Cardiovascular Society class I–III chronic angina pectoris
- Stable post-MI patients
- Asymptomatic patients with objective evidence of myocardial ischaemia
- Angiographically defined CAD, with at least one vessel meeting American Heart Association/American College of Cardiology class I or class II indications for PCI
- Stenosis greater than 80 % in one or more vessels, subtending a large area of myocardium, even in the absence of objective ischaemia

The primary end point of all-cause death or non-fatal MI did not differ between the two groups during a mean follow-

up of 4.6 years [46, 48]. However, in patients who were invasively treated, a symptomatic benefit (freedom from angina) was shown up to 3 years of follow-up.

The conclusions emerging from these data were as follows: (1) PCI is justified if a patient with SCAD has symptoms sufficiently severe to compromise the quality of his/her life; and (2) it is not justified, however, in such patients lacking limiting symptoms.

Still, the fact that more than 35,000 patients were assessed and only 2,200 were included highlights how selective a practitioner must be in clinical application of the data from this trial. Critics of COURAGE point to several flaws. Physicians were permitted to review the angiographic findings prior to allowing enrolment of their patients. It remains unknown how many of these patients were excluded because they were deemed to need PCI on the basi of the angiographic findings, thus confounding a true study of PCI versus OMT.

Also, patient compliance in COURAGE [46] was higher than can be expected in the population at large, as there was excellent adherence to lifestyle changes and excellent rates of patients meeting the goals of LDL, blood pressure, and HbA_{1c} levels, because of the implementation of aggressive nurse case management, and the provision of most medications without cost. Additionally, COURAGE was conducted prior to FDA approval of drug-eluting stents and improved adjunctive pharmacotherapy in PCI; although these therapies have not been shown to decrease death or MI rates, they are associated with lower rates of angina and thus may have decreased hospitalizations.

Other limitations relate to the results themselves: for example, although in the sample size calculation of the COURAGE trial it was expected that crossover would occur in 5 % of subjects over 5 years in patients randomized to OMT, it actually occurred in 33 % [49].

BARI 2D

The BARI 2D trial (n=2,368) evaluated whether PCI or coronary artery bypass grafting (CABG; choice left to the discretion of the treating physician) combined with OMT would be better than OMT alone in patients with SCAD and type 2 diabetes mellitus [2].

This was a complex randomized study in which diabetic patients with SCAD were first separated, on the basis of clinical considerations, into a CABG stratum and a PCI stratum. Within each stratum, patients were randomized to a medical therapy group versus the particular revascularization strategy group. The primary end points were the rate of death and a composite of the rates of death, MI, and stroke.

The study population was quite heterogeneous, since both patients with stenosis greater than 70 % presenting with angina symptoms without documented ischaemia and asymptomatic patients with a positive stress test (approximately 30 % of population) were enrolled. The primary end point was all-cause mortality at 5 years' follow-up, and it did not differ between the two treatment strategies, nor did the rates of MI or stroke. The patients with severest disease were selected for CABG rather than PCI and were a higher-risk group that drew a greater benefit from early revascularization (reduction of MI compared with OMT).

Also in the BARI 2D trial, only a small proportion of screened patients were actually randomized, and this may have implications for the general applicability of the results. Moreover, some of the commonly encountered clinical syndromes were also poorly represented in this study.

The high rate of crossover to revascularization in the OMT group found in COURAGE [46] was possibly higher in BARI 2D (42 %) [2], suggesting that revascularization was merely deferred in almost half of patients randomized to a conservative approach.

Finally, there are some limitations in the interpretation of the findings of COURAGE and BARI 2D. The most debated interpretation applies to these two neutral studies, which had superiority statistical hypotheses that were not met, suggesting that revascularization had no impact on 'hard' outcomes in SCAD patients. However, only BARI 2D was powered for mortality outcome.

FAME 2: Is Fractional Flow Reserve the Light at the End of the Tunnel?

Visual assessment of lesions during coronary angiography has evident limits in defining the functional significance of stenosis. Moreover, the most important outcome-determining factor is the presence and extent of inducible ischaemia [50], which is the rationale for revascularizing such lesions. At the same time, if a stenosis is not flow-limiting, it will not cause angina, and the prognosis with OMT is excellent, with a 'hard' event rate of less than 1 % per year [51].

The functional severity of coronary lesions visualized angiographically may be assessed invasively by measuring intracoronary artery pressure (fractional flow reserve, FFR).

FFR is considered nowadays the gold standard for invasive assessment of physiological stenosis significance and an indispensable tool for decision-making in coronary revascularization [51, 52]. FFR provides guidance to the clinician in situations when it is not clear whether a lesion of intermediate angiographic severity causes ischaemia. Recently, the use of FFR has been upgraded to class IA in multivessel PCI in the ESC guidelines on coronary revascularization [53].

FFR is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperaemia. A normal value for FFR is 1.0, regardless of the status of the microcirculation, and stenoses with an FFR of 0.80 are hardly ever associated with exercise-induced ischaemia [51].

Following the results of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation trial [54], the FAME 2 trial [47••] was designed to mimic COURAGE [45], but to use FFR adjunct to coronary angiography to improve accuracy in identifying lesions that induced ischemia.

In the FAME 2 trial, 888 SCAD patients with functionally significant stenosis (FFR≤0.80) were randomly assigned to FFR-guided PCI plus OMT, or to OMT alone [47••]. The target study population were patients who had at least one functionally significant stenosis and, on average, large areas of ischaemic myocardium (mean FFR value of 0.68), and the low-risk patients with non-ischaemic FFR values were not randomized but were followed in a separate registry. The study was stopped prematurely by the Data Safety Monitoring Board, owing to a highly significant reduction in the rates of hospital readmission and urgent revascularization in the FFR≤0.80 PCI group, compared with the FFR≤0.80 OMT group. There was no difference in the rates of death or MI between the two strategies.

Of 888 patients, 70 (8.4 %) developed at least one primary end point event: 4.3 % in the PCI group and 12.7 % in the medical therapy group ($p<0.001$). Most critically, however, the sole driving force responsible for the differences between the PCI-alone and OMT-alone groups was the rate of urgent revascularization (11 % in the medical therapy group vs 1.6 % in the PCI group; $p<0.001$). There were no differences between the two treatment groups in the incidence of MI and/or death.

Critics of FAME 2 point to the fact that fewer than 70 of the randomized patients were followed up for 12 months. This precludes analysis of longer-term events; thus, it is unknown whether late in-stent thrombosis, in-stent restenosis or de novo lesions would tend to mitigate the differences observed between the OMT and PCI groups. Furthermore, the superiority of the PCI group was driven entirely by a subjective end point (urgent revascularization), and was thus prone to bias, especially in an unblinded study. Not disputable, however, is that half the patients who underwent 'urgent revascularization' had ischemic ECG changes or elevated cardiac enzyme levels, signifying the unequivocal presence of ACS with the need of urgent revascularization.

Because the FAME 2 trial confirmed its primary composite end point, it could be concluded that PCI is indicated in all patients who have stenoses with FFR<0.80.

In conclusion, FFR is an important diagnostic tool in decision-making in SCAD patients, and it can be useful in many different populations, as

- Multivessel disease patients
- Patients with left main stenosis
- 'Post-ACS' patients

The FAME 2 trial did not resolve the revascularization/OMT debate in SCAD patients, but it could represent the light at the end of the tunnel.

Conclusions

The SCAD population is a heterogeneous group of patients both for clinical presentations and for different underlying mechanisms, requiring various degrees of intensity of care. Both medical therapy and coronary revascularization have been shown to improve symptoms and outcomes in this patient population, but on the basis of more recent data, coronary revascularization should be unrestricted only if medical therapy alone is deemed insufficient. Recurrence of symptoms or a high-risk baseline feature suggesting extensive myocardial ischemia should prompt an invasive approach. Aggressive lifestyle and risk factor management remains key in the long-term prognosis of SCAD patients.

Compliance with Ethics Guidelines

Conflict of Interest Marco Valgimigli and Simone Biscaglia declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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