Revista da SOCESP
Sociedade de Cardiologia do Estado de São Paulo



# EVOLUTION OF TREATMENT FOR STABLE CORONARY ARTERY DISEASE – MORE PHYSIOLOGICAL, LESS INVASIVE

## EVOLUÇÃO NO TRATAMENTO DA DOENÇA CORONÁRIA ESTÁVEL - MAIS FISIOLÓGICO, MENOS INVASIVO

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Received on 02/03/2018,
Accepted on 02/25/2018

## ABSTRACT

Some concepts regarding the clinical management of coronary artery disease (CAD) have radically changed over the past decades. Initially focused on improving ischemic symptoms, today, optimal medical therapy is fundamental for reducing cardiovascular events. In the same time frame, there has been an immense development in revascularization treatment. Coronary angioplasty has become one of the most frequently performed therapeutic interventions, and myocardial revascularization techniques have been the subject of more randomized clinical trials than any other intervention in medicine. Furthermore, several invasive and non-invasive imaging modalities have been developed, enabling more accurate study of coronary artery disease, recognition of prognostic markers, clearer patient evaluation, and earlier treatment indications.

**Keywords:** Coronary disease; Treatment; Myocardial revascularization.

## RESUMO

*Ao longo das décadas, alguns conceitos mudaram radicalmente a respeito do tratamento clínico da doença arterial coronariana (DAC). Inicialmente focado na redução dos sintomas isquêmicos, hoje a otimização da terapêutica clínica é fundamental para a redução de eventos cardiovasculares. No mesmo período, houve um grande desenvolvimento das técnicas de revascularização. A angioplastia coronária tornou-se uma das intervenções terapêuticas mais frequentemente realizadas e as técnicas de revascularização miocárdica vêm sendo objeto de mais ensaios clínicos randomizados, do que qualquer outra intervenção em Medicina. Ainda mais, várias modalidades de imagem invasivas e não invasivas foram desenvolvidas, permitindo estudar com maior precisão a doença arterial coronariana, reconhecer novos marcadores prognóstico, avaliar mais claramente os pacientes e indicar mais acertadamente o tratamento.*

***Descritores:*** *Doenças coronárias; Tratamento; Revascularização miocárdica.*



In the recent decades, there have been major advances in the interventional treatment of coronary artery disease (CAD). Coronary artery bypass graft (CABG) surgery was first performed just over 50 years ago, and the 40th anniversary of the first coronary angioplasty performed in 1977 by Dr. Gruentzig was celebrated in 2017.[1] Since then, the two revascularization techniques, surgical and percutaneous, have undergone significant advances, such as the use of arterial grafts in revascularization surgery and the advent of stents in interventional cardiology. Currently, coronary angioplasty is one of the most frequently performed therapeutic interventions, and myocardial revascularization techniques have been the object of more randomized clinical trials than any other medical intervention.[2]

Simultaneously, the advances in pharmacological therapy have revolutionized the approach to CAD. The so-called optimal medical therapy (OMT), which refers not only to the use of medications but also to the lifestyle changes that reduce the risk of cardiovascular events, is the basis of care for these patients.[3]

## OPTIMAL MEDICAL THERAPY: FOCUSING ON PATHOPHYSIOLOGY TO REDUCE EVENTS

Over time, some concepts of medical therapy (MT) for CAD have radically changed. Although initially focused on reducing ischemic symptoms, today MT optimization is crucial for reducing cardiovascular events and targeting various mechanisms involved in atherothrombotic events. OMT is recommended for all patients with CAD and is the initial treatment strategy indicated for patients with stable CAD.[4] Despite some divergences between clinical trials, the optimal treatment of CAD should include, in addition to anti-ischemic medication for symptom control, an antiplatelet agent, a statin, an angiotensin-converting enzyme (ACE) inhibitor [or Angiotensin II receptor blocker (ARB)], and a beta-blocker (BB).

Despite significant and clinically important reductions in morbidity and mortality, the literature shows that MT for

secondary prevention of CAD remains underused. The international Reduction of Atherothrombosis for Continued Health (REACH) registry, including 37,154 patients with atherosclerotic disease, showed that only half of them were receiving OMT (46.7% at baseline and 48.2% at one-year evaluation).[5] In low-income countries, the use of drugs for secondary prevention in CAD is even lower, with less than 10% patients receiving, for example, statins.[6]

A *post hoc* analysis of the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) trial showed that only one third of the patients were receiving OMT, defined as the combination of at least an antiplatelet, a statin, a BB, and an ACE inhibitor/ARB, at the five-year follow-up.[7] In this trial, the lack of OMT was associated with increased mortality and combined death, acute myocardial infarction (AMI), and stroke in the five-year follow-up. The treatment effect of OMT (36% relative reduction in mortality with OMT vs. without OMT) was stronger than the treatment effect of the revascularization strategy (26% relative reduction in mortality with myocardial revascularization vs. percutaneous coronary intervention), most likely because of the beneficial effects of OMT in slowing CAD progression and in decreasing the susceptibility to new plaque ruptures in untreated or revascularized coronary segments. This underlines the importance of using OMT in CAD and the need for specific interventions to optimize its prescription and patients' adherence.

Some patients will experience an adverse event even if they are optimally treated. Over five years, 21.2% of patients treated with a statin experienced a major cardiovascular event in a meta-analysis of 14 randomized clinical trials comparing statin versus placebo treatments in approximately 29,000 patients with cardiovascular disease (CVD).[8] The factors associated with the residual risk of an adverse event were explored among 9251 patients with CAD and low-density lipoprotein-cholesterol (LDLc) < 130 mg/dL treated with atorvastatin in the Treating to New Targets (TNT) trial. In multivariate analysis, advanced age, high body mass index, male sex, hypertension, diabetes mellitus, and baseline apo-lipoprotein B and urea levels were identified as significant risk factors of adverse events.[9] These findings highlight the relevance of aggressive treatment of all modifiable risk factors in patients with established CAD. Data analysis of diabetic patients in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D), and Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trials found that only 8%, 18%, and 23% of patients from FREEDOM, COURAGE, and BARI-2D trials, respectively, reached the blood pressure, cholesterol and glycemia control, and tobacco smoking cessation targets.[10]

## Anti-ischemic treatment

Antianginal therapy is based on the use of anti-ischemic drugs alone or in combination. BBs are the first-line therapy to reduce angina episodes and to improve exercise tolerance because they have also been shown to reduce mortality in some subgroups of patients with CAD.[11] Nitrates are also used to alleviate anginal symptoms, although no evidence of decreased mortality with their use was found. Some deleterious effects from the chronic use of long-acting nitrates have been described, such as worsened endothelial dysfunction due to sympathetic nervous system and renin-angiotensin-aldosterone system activation, as well as increased endothelin and superoxide production and phosphodiesterase activity.[12] However, the clinical impact of these alterations remains unknown. Calcium channel blockers (CCBs) are essentially vasodilator drugs with no known benefits in reducing cardiovascular events, which are especially indicated in cases of BB contraindication and in variant or vasospastic angina (Prinzmetal).[11] These three classes remain the drugs of choice for reducing anginal symptoms, although other drugs with different mechanisms of action, such as trimetazidine and ranolazine, may also help in treating patients with more refractory symptoms. It should be noted that, in stable chronic CAD, the use of these anti-ischemic medications is not associated with reduced cardiovascular mortality.

OMT in patients with stable angina obviously involves more than antianginal therapy. Treatments that reduce the incidence of cardiovascular events should be started promptly. This includes not only drug treatments, but also dietary and lifestyle interventions. These therapies are aimed at reducing plaque progression, stabilizing the plaque, reducing inflammation, and preventing thrombosis if plaque rupture or erosion occurs. Drugs that reduce death or cardiovascular events in patients with CAD include antiplatelet drugs, statins, renin-angiotensin system inhibitors, and BB. All these agents have been shown to improve clinical outcomes and are recommended as secondary prevention therapy in patients with clinical evidence of CAD.



## Lipid-lowering agents

Statins are the mainstay of cardiovascular risk reduction therapy in patients with CAD. Large randomized clinical trials have shown benefits of statin therapy in patients with established CVD across a broad spectrum of baseline LDLc levels. Significant and clinically important decreases in AMI, cerebrovascular accident (stroke), and cardiovascular death rates were shown in more than 130,000 patients randomized to statin versus placebo and in more than 40,000 patients randomized to intensive statin therapy versus usual doses of statins, with a 10% decrease in all-cause mortality for every 40 mg/dL decrease in LDLc.[13] The decrease in major cardiovascular events with the use of statins is directly proportional to the absolute decrease in LDLc.[14,15] In these clinical trials, lower LDLc values were associated with better outcomes, with no clear threshold below which incremental benefits are no longer observed. In all 26 trials, all-cause mortality decreased by 10% for every 1.0 mmol/L decrease in LDLc (rate ratio 0.90, 95% confidence interval 0.87–0.93; $p < 0.0001$).

Nevertheless, the question as to whether statin therapy should aim to achieve a specific LDLc level or be based on therapy potency remains unanswered. Although some guidelines recommend reaching specific LDLc goals, in rather absolute or percentage values,[4] others indicate the use of evidence-based doses of high-potency statins, regardless of baseline LDLc values.[16]

Among other lipid-lowering therapies, only ezetimibe and PCSK9 inhibitors (evolocumab) reduced cardiovascular outcomes,[17-19] although, in both cases, in patients at high

cardiovascular risk already using statins. Therefore, these medications should be combined with a statin to reduce the risk factors in these populations.

## Antiplatelet therapy

Acetylsalicylic acid (ASA) remains the main pharmacological drug for arterial thrombosis prevention, reducing the risk of myocardial infarction, stroke, and cardiovascular death among patients with a wide range of cardiovascular manifestations. The benefits from ASA in secondary prevention were shown by meta-analyses that included data on more than 135,000 patients from 195 randomized clinical trials.[20] Antiplatelet therapy significantly reduced the relative risk of vascular events (nonfatal AMI, nonfatal stroke, and cardiovascular death) by approximately 22%. No significant differences in efficacy or safety were found between the doses ranging from 75 to 150 mg/day (low-dose aspirin) and those ranging from 160 to 325 mg/day.

Long-term treatment with ASA is recommended for patients with CAD. Clopidogrel can be used as an alternative for patients who cannot take ASA and for those with a history of gastrointestinal bleeding.[21] Conversely, dual antiplatelet therapy (DAPT), combining a P2Y12 receptor inhibitor with ASA, is recommended for a subgroup of patients after acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) with stent implantation, because this treatment is highly effective in stent thrombosis prevention. This is one of the most intensely researched therapeutic interventions in cardiology, with more than 35 randomized clinical trials including more than 225,000 patients.[22] Extended DAPT, for more than one year after PCI or AMI, may also be prescribed, mostly reducing the rate of spontaneous (stent-unrelated) AMI, albeit associated with an increased risk of bleeding. Because the benefits from DAPT apparently depend on cardiovascular history (ACS vs. stable CAD), an individualized approach, adapting the duration of the DAPT according to the ischemic and bleeding risk assessment of each patient using scores specifically designed for this purpose, may be useful.[22]

Other antiplatelet agents that have shown benefits in reducing risks in secondary prevention include prasugrel and ticagrelor. Their early anti-ischemic benefits were higher than those of clopidogrel added to ACS, albeit with a risk of major bleeding due to a more potent antiplatelet effect during chronic treatment. In the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38), which showed the superiority of prasugrel over clopidogrel, the pharmaceutical agents were administered only after coronary angiography and therefore, prasugrel should not be administered before the procedure.[23] For patients at risk of early CABG surgery, P2Y12 receptor blocker administration can be postponed until knowing the coronary anatomy, and ticagrelor or prasugrel is recommended in these cases.

The PLATelet inhibition and patient Outcomes (PLATO) trial assessing ACS had already shown that ticagrelor, a P2Y12 platelet receptor inhibitor, was more effective than clopidogrel, when combined with aspirin, in reducing cardiovascular events.[24] However, its role in long-term secondary prevention remains unclear. In the PEGASUS trial, 21,162 patients with myocardial infarction that occurred within 1–3 years before starting the study were randomized to receive, in addition to aspirin, 90 mg of ticagrelor twice daily (the same dose as that recommended post AMI), 60 mg ticagrelor twice daily, or placebo. Both doses similarly reduced the risk of risk of cardiovascular death, myocardial infarction, or stroke (by approximately 15%) compared with placebo, and increased the risk of major bleeding.[25] This trial justified the US Food and Drug Administration (FDA) approval of 60 mg ticagrelor for risk reduction in the secondary prevention in individuals with prior AMI. More recently, rivaroxaban, a factor Xa inhibitor, showed benefits in reducing cardiovascular events in individuals with stable atherosclerotic disease when combined with aspirin compared with placebo.[26] The dose used, 2.5 mg twice daily, was lower than the dose commonly used in the prevention and treatment of thromboembolic events.

In addition to aspirin and clopidogrel, other drugs with antiplatelet or antithrombotic action have shown efficacy in reducing cardiovascular risks, although they are not yet approved in Brazil for this purpose. Vorapaxar is an antiplatelet agent that prevents thrombin receptor-activating peptide (TRAP)-induced platelet aggregation by selective inhibition of the protease-activated receptor 1 (PAR-1). In the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2P–TIMI 50), 26,449 patients in secondary prevention (nearly 80% with CAD) were randomized to receive vorapaxar or placebo, in addition to standard therapy, including DAPT with aspirin and a thienopyridine, when appropriate. In spate of increasing the incidence of intracranial bleeding, the use of vorapaxar was associated with a 13% reduction in the incidence of the primary composite outcome of cardiovascular death, myocardial infarction, stroke, or recurrent ischemia leading to urgent coronary revascularization.[27]

## Renin-angiotensin system inhibitors

ACE inhibitors were found to reduce total mortality, myocardial infarction, stroke, and heart failure in specific subgroups of patients, including those with heart failure, previous AMI, diabetes mellitus, and renal disease with proteinuria.[21]

The Heart Outcomes Prevention Evaluation (HOPE) trial was the first trial to consistently show that an ACE inhibitor may reduce cardiovascular risks, even in the absence of heart failure and left ventricular dysfunction. In this clinical trial that included 9,541 patients, nearly 80% with chronic CAD, the use of ramipril was associated with a 22% reduction in the risk of cardiovascular death, AMI, and stroke.[28] In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), telmisartan, an ARB, was evaluated in the same high-risk population setting (75% with established CAD) in comparison with and in addition to ramipril.[29] The risk reduction was similar to that assessed with ramipril, although the combination of both had no additional risk reduction effect and increased the incidence of adverse events.

Although the two previous trials had assessed large populations of patients with chronic CAD, in the EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA), the study population exclusively consisted of patients with stable CAD with heart failure (12,218 patients). The use of perindopril

reduced the same primary outcome as that evaluated in the HOPE trial by 20%.[11]

Therefore, ACE inhibitors should be considered in the treatment of patients with CAD, especially in those with hypertension, diabetes mellitus, chronic kidney disease, or ejection fraction < 40%. Approximately 20% of patients with stable CAD may not have any of these indications, and the evidence of benefits from ACE inhibitors is less convincing in these patients.[30] The use of ARBs may be an alternative for patients with CAD when the ACE inhibitors are indicated, but not tolerated.

### Beta-blockers

In addition to their effectiveness in reducing the severity and frequency of angina symptoms, BBs reduce mortality in patients with stable CAD with a history of AMI or in patients with a reduced ejection fraction.[31,32] However, no high-quality evidence of improvement in survival or reduction in AMI incidence by BBs has been found outside of these subgroups.

## COMPARISON BETWEEN PHYSIOPATHOLOGY-FOCUSED OPTIMAL MEDICAL THERAPY AND INVASIVE TREATMENT

A comparison between medical and interventional therapies in stable CAD has been performed in several clinical trials, in order to identify the patients who show improved prognosis when undergoing (surgical or percutaneous) myocardial revascularization, in addition to OMT. However, with the rapid advances in this field of cardiology, the results of older clinical trials should always be analyzed with caution. The medications have improved, the pathophysiological aspects of atherothrombotic disease previously overlooked are now addressed by MT and, similarly, both surgical and percutaneous myocardial revascularization techniques have advanced, particularly the stents used.

Because it was the first invasive strategy developed to treat CAD, CABG surgery was long used without actual evidence of increased survival among patients with CAD. Subsequently, the Coronary Artery Surgery Study (CASS) randomized 780 patients with stable CAD to surgical or non-surgical treatment and showed that the subgroup of patients with tri-arterial CAD and an ejection fraction < 50% showed improved prognosis when submitted to myocardial revascularization in addition to OMT.[33] In general, revascularization improves the prognosis in the most severe patients, especially in those with multi-arterial disease, in the presence of left ventricular dysfunction, and/or large ischemic area.

The Brazilian study Medical, Angioplasty or Surgery Study II (MASS II) was the only randomized, controlled clinical trial that compared MT with PCI (72% of patients treated with conventional stent implantation and 28% of patients treated with balloon angioplasty) with CABG surgery in patients with multi-arterial CAD.[34] A total of 611 patients with stable angina and preserved ventricular function were followed in a single center. After a 10-year follow-up, patients subjected to CABG surgery showed better results. The primary outcome (composite outcome of death, AMI with ST-segment elevation, or refractory angina requiring revascularization) occurred in 33.0% of patients subjected to CABG surgery, 42.4% of patients in the PCI group, and 59.1% of patients in the MT group ($p < 0.001$). However, the long-term survival rates were similar among the three groups (74.9% in CABG surgery, 75.1% in PCI, and 69% in MT groups at 10 years, $p = 0.089$). In the 10-year follow-up, the AMI rates were 10.3% with CABG, 13.3% with PCI, and 20.7% with MT ($p < 0.01$), the additional revascularization rates were 7.4% with CABG, 41.9% with PCI, and 39.4% with MT ($p < 0.001$), and the angina-free rates were 64% with CABG, 59% with PCI, and 43% with MT ($p < 0.001$). However, extrapolating the results from the MASS II trial to the current practice is difficult, considering the improved performance of pharmacological stents and the considerable MT changes (for example, statins were used by only 63% of patients then).

Conversely, the COURAGE trial assessed whether percutaneous revascularization (angioplasty with stent implantation) combined with OMT would be better than OMT alone. In total, 2287 patients with stable CAD and evidence of ischemia and significant disease in at least one coronary artery were included in the clinical trial. Of them, 87% were symptomatic and 58% had class II or III angina. Thus, all patients received OMT. In a mean follow-up of 4.6 years, no significant difference in the primary outcome of all-cause death and non-fatal myocardial infarction (with approximately 19% AMI in both groups) was found between both treatment strategies. Furthermore, no significant difference in the hospitalization rates for ACS (approximately 12% in both groups) was found. Significantly fewer patients from the PCI group were subjected to additional revascularization procedures (21% vs. 33%, hazard ratio 0.60, 95% confidence interval 0.51–0.71). In a report of the results from a 15-year follow-up (with a mean of 6.2 years) of 1121 participants, no significant difference in death rates was found between both groups (24% and 25%, respectively).[35]

Most meta-analyses have found no evidence of increased survival or reduced myocardial infarction rates due to angioplasty. However, a key limitation of most of these studies is the lack of use of drug-eluting stents. In comparison with conventional and first-generation drug-eluting stents, the new-generation drug-eluting stents improved the safety outcomes, including death, myocardial infarction, and stent thrombosis rates.[36-38] In a 2014 meta-analysis, which evaluated 95 clinical trials (n = 93,553 patients) towards assessing whether revascularization improves the prognosis compared to MT in patients with stable CAD, both CABG surgery (rate ratio 0.80, 95% confidence interval 0.70–0.91) and new-generation drug-eluting stents [everolimus: rate ratio 0.75, 95% confidence interval 0.59–0.96; zotarolimus (Resolute): rate ratio 0.65, 95% confidence interval 0.42–1.00], but not balloon angioplasty or conventional and first-generation drug-eluting stents, were associated with significant survival benefits.[39]

Furthermore, the presence and extension of ischemia are other key prognostic factors in CAD. Although coronary angiography is considered the gold standard in the evaluation of coronary lesions, its ability to establish the functional significance of obstructions is limited. Fractional flow reserve (FFR) is a technique that can be performed during coronary angiography, allowing invasive identification of ischemic lesions. In the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME-2) trial, patients with

stable CAD and at least a functionally significant stenosis (FFR ≤ 0.80) were randomized to MT alone or additional FFR-guided PCI. The clinical trial was prematurely interrupted after including 888 patients because of a significantly higher incidence of the primary outcome (composite outcome of death, myocardial infarction, and urgent revascularization) in the FFR-guided PCI group. The final analysis showed a 4.3% primary outcome incidence in the PCI group and 12.7% in the MT group ($p < 0.001$), albeit with no significant difference in death or myocardial infarction rates between the two groups.[40] In a meta-analysis that included only patients with documented myocardial ischemia (n = 1557) from three randomized clinical trials [FAME 2, COURAGE nuclear substudy, and Swiss Interventional Study on Silent Ischemia Type II (SWISS 2)], PCI was associated with a decreased all-cause mortality rate (hazard ratio 0.52, 95% confidence interval 0.30–0.92) in a mean follow-up of three years.[41] Thus, a subgroup of patients with stable CAD may benefit from PCI for increased survival, similarly to those with moderate-to-severe ischemia.

When questioning whether revascularization should be performed in intermediate stenoses with no prior non-invasive physiological data guiding decision-making, FFR is the standard technique for invasive physiological assessment of the hemodynamic significance of intermediate stenoses and should be measured.[42] Recently, the instantaneous wave-free pressure ratio (iFR), an FFR surrogate that assesses the severity of coronary stenosis without the need for inducing maximal myocardial hyperemia with adenosine, was developed and tested. In two noninferiority trials that randomized patients to iFR- or FFR-guided revascularization (cutoffs 0.89 and 0.80, respectively), the primary composite outcome (death, AMI, and unplanned revascularization) occurred at similar frequencies in both one-year follow-up groups.[43,44]



## THE USE OF NEW DIAGNOSTIC TECHNIQUES IN THE IDENTIFICATION OF UNSTABLE PLAQUES

Thanks to technological advances that enabled the visualization and localized treatment of atherosclerotic plaques, considerable efforts have been made to recognize "vulnerable plaques", defined as plaques prone to cardiovascular events. Pathologival studies have shown that ACS is most often caused by plaque rupture (in approximately 73% of cases), although plaque erosion or thrombus formation in calcium nodules may also cause ACS.[45] Most lesions that will eventually rupture show specific morphological findings, collectively termed thin-cap fibroatheroma (TCFA).[46] Because TCFA has specific phenotypic characteristics, many hoped that its early identification would enable the detection of vulnerable lesions and the potential identification of high-risk patients.

Over the last few years, several invasive and noninvasive imaging modalities have been developed to more accurately study CAD. Intracoronary ultrasound (ICUS) was the first imaging modality that enabled *in vivo* plaque composition evaluation, deepening the understanding of the atherosclerotic process. ICUS allows accurate evaluation of the plaque phenotypic characteristics and is an important tool for the identification of vulnerable lesions. However, prospective studies have raised questions about its accuracy. Although ICUS was able to predict future events, its positive predictive value was quite low, ranging between 18.2–41%.[47,48] Optical coherence tomography (OCT), with its high-resolution images (10–20 $\mu$m vs. 150 $\mu$m with ICUS), enables a more detailed plaque morphology evaluation and visualization of micro-characteristics associated with increased vulnerability, such as plaque erosion, presence of macrophages, neovascularization, and microcalcifications, which cannot be detected by ICUS. However, OCT also has significant limitations, including a low penetration depth of 2–3 mm and the failure to provide a reliable assessment of the plaque distribution in the geometry of the vessel.

The combined intravascular imaging seems capable of overcoming the individual limitations of each method and of providing a more reliable characterization of the plaque composition. Combined ICUS-OCT evaluation was used in patients with ACS to compare plaques of the culprit lesion with plaques associated with a silent rupture ("silent" plaques), finding a smaller luminal area and a greater plaque load in lesions that ruptured and caused events.[49] In another study of the same group, the plaque morphology of angiographically significant (stenosis > 70%), moderate (stenosis 50–69%), and discrete (stenosis 30–49%) lesions was assessed by ICUS-OCT. Significant stenoses were associated with a more vulnerable phenotype, a higher prevalence of TCFA and thin fibrous layers, and higher plaque load than mild or moderate stenoses.[50] These findings showed that lesions with severe stenoses are more prone to rupture and to cause events than are those with mild or moderate stenoses,[51,52] questioning the results of angiographic studies conducted in the 1980s, which suggested that AMI is most likely caused by non-significant stenoses.[53] These results raised hopes that hybrid imaging may allow more accurate assessment of plaque morphology and prediction of lesions that will progress and cause cardiovascular events.

However, the significance of the treatment of rupture-prone plaques remains unclear because several vulnerable plaques usually coexist in patients at risk. Furthermore, some studies suggested that plaques may alternate between vulnerable and non-vulnerable phenotypes, thus suggesting that non-vulnerable plaques may become morphologically unstable and undergo rupture or erosion.[54] Coronary angiotomography studies support this hypothesis, because they found similar cardiovascular death and AMI rates in patients with extensive non-obstructive CAD (hazard ratio 3.1) and in patients with non-extensive obstructive CAD (hazard ratio 3.0), thus showing the additional prognostic value of plaque extension, regardless of whether CAD is obstructive or non-obstructive.[55] Thus, the number of non-culprit, asymptomatic plaques with potential for transformation into vulnerable plaques may be significant, especially in cases of high atherosclerotic load. These facts are in favor of implementing systemic approaches to treat patients with CAD primarily focused on atherosclerotic disease burden, rather than on individual plaque characteristics.[56]

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest relevant to this study.

AUTHOR CONTRIBUTIONS: Each author individually and significantly contributed to this manuscript. JRFN and ACPC were involved in the study design. CS and AB performed the literature review and were the main authors of the manuscript. JRFN, ACPC, and CS critically reviewed the manuscript.

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