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EDITORIAL

Outcomes Following Plaque Erosion-Based Acute Coronary Syndromes Treated Without Stenting: The Plaque Matters

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Acute coronary syndrome (ACS) remains a major cause of morbidity and mortality across the world.[1] The 2 major causes of ACS are plaque rupture and plaque erosion. The incidence of plaque erosion has been increasing in association with reduction in lipid levels and vascular inflammation driven by the increasing use of statin therapy, resulting in a change of the atherosclerotic phenotype.[2–4]

See Article by Yin et al.

Clinical and basic science research indicates that plaque erosion is a distinct pathogenic and clinical entity.[4] Plaque erosion is characterized by an intact fibrous cap and a larger vessel lumen than plaque rupture, as well as by the presence of a platelet-rich thrombus and neutrophil infiltrates. Clinically, plaque erosion is associated with a better risk profile and outcomes compared with plaque rupture.[5,6] The recent application of advanced intracoronary imaging modalities, such as high-resolution optical coherence tomography (OCT), has provided valuable insights into plaque features characterizing plaque erosion thrombosis in patients with ACS, and further offers the opportunity to tailor the management of these patients.

While the current clinical standard for ACS culprit lesions is to offer coronary revascularization, including percutaneous coronary intervention (PCI) or coronary artery bypass grafting, the recent EROSION (Effective Anti-Thrombotic Therapy Without Stenting: Intravascular Optical Coherence Tomography-Based Management in Plaque Erosion) study has challenged this dogma for patients with plaque erosion.[7] The EROSION study was motivated by the primary concern that PCI with drug-eluting stents carries a nontrivial risk of stent thrombosis and long-term indefinite rate of target lesion revascularization because of restenosis, neoatherosclerosis, and late stent thrombosis.[8] Interestingly, a serial OCT imaging investigation has suggested that plaque erosion underlies an impaired vascular response to stenting after drug-eluting stent implantation,[9] further raising interest in a stent-avoidance strategy for patients with ACS with plaque erosion.

The relatively small single-arm EROSION study of 55 patients was a first proof-of-concept, prospective and pilot study designed to explore the feasibility and safety of antithrombotic therapy without stenting in patients with OCT-determined plaque erosion. Plaque erosion was defined as the observation of thrombus, typically platelet-rich white thrombus, overlying an intact fibrous cap.[2] In the EROSION study, patients with ACS were enrolled if OCT confirmed the presence of plaque erosion, the angiographic residual vessel

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stenosis was not >70%, and the TIMI (Thrombolysis in Myocardial Infarction) flow grade was 3. Patients underwent baseline OCT and then follow-up OCT in 1 month to detect a 50% reduction in the thrombus volume, the primary end point of the study. Of note, most patients underwent thrombectomy and received glycoprotein IIb/IIIa antagonists during PCI, and were prescribed ticagrelor along with aspirin for dual antiplatelet therapy for 1 year. At the 1-month follow-up OCT study, 78.3% of patients had a ≥50% decrease in thrombus volume and 92.5% of the conservatively treated patients were free of major adverse cardiovascular events (MACE).[7] However, the 4-year follow-up analysis of the EROSION study reported that the incidence of MACE rose to 23%, largely related to nonurgent target lesion revascularization that was not associated with death, heart failure, stroke, recurrent myocardial infarction, unstable angina-induced rehospitalization, or coronary artery bypass grafting.[10]

Given these provocative findings that clinicians might be able to defer stent-based PCI for a subset of patients with ACS with plaque erosions, further investigations utilizing larger sample sizes, broader populations, and randomized controls are of substantial interest. In this issue of the *Journal of the American Heart Association* (*JAHA*), Yin and colleagues present their findings from a larger population of 252 patients with ACS with plaque erosion phenotype, including 55 patients from the original EROSION study.[11] This study was a single-center observational study comprising subjects who met the inclusion criteria of the EROSION study. The goal of this study was to assess baseline clinical, angiographic, and OCT-based predictors of MACE following a nonstenting PCI strategy. After excluding 20 patients with premature dual antiplatelet therapy discontinuation, suboptimal OCT images, prior stent or coronary artery bypass grafting, or lost to follow-up (n=4), 232 patients remained in the final analysis.

PCI was performed using manual aspiration thrombectomy in ≈75% of patients, and ≈50% of patients received glycoprotein IIb/IIIa antagonists for 12 to 24 hours. All patients were preloaded with dual antiplatelet therapy with ticagrelor and received IV heparin before PCI. OCT was performed per protocol (no predilatation was allowed to avoid balloon-induced plaque disruption) and images were analyzed at a core laboratory. Plaque erosion was identified by the presence of attached thrombus overlying an intact plaque, or in the absence of thrombus, by detection of a luminal surface irregularity at the culprit lesion, or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately adjacent to the thrombus site.

Patients were then stratified based on MACE or no-MACE. At a median follow-up of 2.9 years, 50 of 232 patients (21.6%) developed MACE, including 6 patients (2.6%) with cardiac death, 3 patients (1.3%) with nonfatal reinfarction, 29 patients (12.5%) with target lesion revascularization, 36 patients (15.5%) with rehospitalization because of angina pectoris, 2 patients (0.9%) with severe bleeding, and 5 patients (2.2%) with stroke. In their report, patients who experienced MACE were older, and had a higher degree of percentage of area stenosis (72% versus 64%, $P<0.001$) and thrombus burden (24% versus 20%, $P=0.010$) revealed by OCT at baseline. Multivariate Cox regression analysis confirmed that age, percentage of area stenosis, and thrombus burden were predictors of MACE. Receiver operating curve analysis disclosed that the cutoff values of predictors were age ≥60 years, percentage of area stenosis ≥63.5%, and thrombus burden ≥18.5%, respectively, and when they were all present, the rate of MACE rose to a very high level of 58% (hazard ratio, 4.22, $P<0.001$).

Regarding dual antiplatelet therapy, most patients received ticagrelor and the remaining minority (≈25%) received clopidogrel. While there were no meaningful differences in MACE rates between the dual antiplatelet therapy groups, it would be interesting to analyze the MACE rates in the clopidogrel group based on clopidogrel genotype and responsiveness.[12] In the 4-year EROSION study follow-up, patients with a poor response to antithrombotic therapy and smaller reduction in thrombus volume in the first month were more likely to require target vessel revascularization.[10] In addition, a multivariate analysis of the EROSION study showed that the use of glycoprotein IIb/IIIa inhibitors and thrombus score were negative and positive independent predictors of residual thrombus, respectively.[13] Therefore, further studies are required of the optimal antithrombotic and antiplatelet regimen best suited to treat plaque erosion, particularly given the overall high MACE rate (21% at 2.9 years in the current study, a higher rate than the original EROSION study of 23% at 4 years). Might the use of short-term anticoagulation (ie, low-dose rivaroxaban)[14] benefit patients with plaque erosion? In addition, given the essential role of endothelial cell loss (desquamation) in plaque erosion,[4] could pro-endothelial pharmacotherapies such as angiotensin-converting enzyme inhibitors be helpful?[15] Finally, another open question is whether balloon angioplasty alone, or drug-coated balloon angioplasty, might be effective for plaque erosion; such an approach might still avoid a stent-based strategy for the majority of patients, but provide a lower area of stenosis, a driver of future MACE.

There are some limitations of this study. First, as acknowledged, this was a single-center, single-arm, unblinded prospective study. The study population exhibited a high predominance of ST-segment–elevation myocardial infarction (80%) compared with non-ST-segment–elevation myocardial infarction, similar to the original EROSION study, but may not fully reflect the non-ST-segment–elevation myocardial infarction population where erosion is likely to play a predominant role.[4] Furthermore, there was a wide utilization of glycoprotein IIb/IIIa inhibitors and manual aspiration thrombectomy; their routine use is not recommended by current clinical practice guidelines in patients with ACS. OCT, while exhibiting superior resolution compared with intravascular ultrasound, is limited by depth penetration (particularly in the setting of red blood cell–rich "red" thrombus) and precise tissue characterization; therefore, the accuracy of detecting plaque erosion by OCT remains limited. One exciting opportunity to improve OCT diagnosis of erosion is to couple intracoronary near-infrared fluorescence molecular imaging with OCT.[16,17] Given the unique molecular physiology underlying plaque erosion (higher toll-like receptor 2, neutrophil, and myeloperoxidase, hyaluronidase expression),[18] near-infrared fluorescence-OCT strategies may emerge to improve the diagnosis of plaque erosion. In addition, the use of noninvasive imaging to assess residual lumen caliber, and the use of blood biomarkers, as elegantly outlined by Fahed and Jang, appears intriguing.[4]

While PCI or surgical revascularization remains the standard-of-care for ACS patients with severe CAD, regardless of plaque phenotype, we congratulate Yin and colleagues for providing new insights into MACE features for patients with plaque erosion. The study extends the general safety and feasibility of a nonstenting strategy, and highlights the potenital for a more individualized "precision medicine" approach to plaque erosion. Along these lines, the elegant analysis of the predictors of MACE (age ≥60 years, percentage of area stenosis ≥63.5% and thrombus burden ≥18.5%) may help identify patients not suitable for a conservative strategy. To further this field, ongoing efforts in 3 major areas of research are needed: development of reliable imaging and blood biomarkers to detect "vulnerable" plaques at risk of developing an erosive phenotype; identifying optimal pharmacotherapeutics for treating plaque erosion; and performance of well-powered randomized clinical trials comparing medical therapy to revascularization.

ARTICLE INFORMATION

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