EDITORIAL COMMENT

Prediction of MACE After ACS
Demographics and Angiography Versus Imaging*

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Yesterday is not ours to recover,
but tomorrow is ours to win or to lose
—Lyndon B. Johnson (1)

Current prevention of major adverse cardiovascular events (MACE) after acute coronary syndromes (ACS) is based on aggressive medical therapy, and guideline-driven treatment of traditional coronary risk factors. These include achieving low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood pressure, and glycosylated hemoglobin target levels, smoking cessation, and physical activity. In patients with left ventricular ejection fraction below 40%, the use of an angiotensin-converting enzyme inhibitor is recommended, and in patients with left ventricular ejection fraction below 35% an automatic implantable cardioverter-defibrillator should be considered (2).

This universal therapeutic approach is based on a practical concept: All patients after an ACS diagnosis must receive aggressive, goal-oriented medical therapy to reduce recurrent events. If coronary risk factors are successfully treated, further risk stratification with biomarkers or novel imaging technology may not change therapy. In summary, the current practice of secondary prevention after ACS is purely based on traditional medicine, and does not necessarily include additional testing. Nevertheless, even with second-generation P2Y12 inhibitors, MACE rates are significant, reaching 9% to 14% during the first 12 to 17 months (3,4). Therefore, clinical practice of secondary prevention after ACS has a significant opportunity for improvement. The question is how.

Identifying Patients at Risk for MACE After ACS

Cardiovascular death, myocardial infarction, and repeat revascularization after ACS are equally divided between events related to the culprit lesion (restenosis, stent thrombosis) and events related to nonculprit lesions (NCL). Within the first group, drug-eluting stents contributed significantly, and bioabsorbable stents may offer modest advantages (5). However, there is little room for improvement in this group. The great opportunity lies in identifying and treating patients with high-risk NCL responsible for future MACE.

Recently, several intracoronary and noninvasive imaging studies using multivessel intravascular ultrasound (IVUS) with radiofrequency backscattered analysis or computerized tomography have properly identified high-risk, nonculprit, thin-cap fibroatheroma (TCFA) responsible for future MACE in patients with ACS or angina pectoris (6–9). However, a direct link between clinical data and high-risk TCFA is missing.

Although recent observational studies suggest that an aggregate approach using biomarkers for inflammation, cell stress, and coagulation may help to identify patients at increased risk for recurrent events (10), more traditional approaches including the GRACE (Global Registry of Acute Coronary Events), CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes), and TIMI (Thrombolysis In Myocardial

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Infarction) scores are commonly used. However, these scores are derived from demographic factors that may be ubiquitously distributed in the ACS population. An aggregate approach, using a combination of noninvasive biomarkers and invasive imaging to predict high-risk plaques, is yet another possible strategy and was used in a paper in this issue of *iJACC*.

**The Present Study**

In this issue of *iJACC*, Bourantas et al. (11) evaluated the predictive value of the Framingham risk score plus angiography to identify patients with documented high-risk, nonculprit TCFA. Using the 3 IVUS-derived morphologic predictors of MACE, this subanalysis of the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study compared the Framingham risk score (FRS) in patients with high-risk (≥2 predictors) NCL versus patients with low risk (≤1 predictor). Angiographic data were also included to improve prediction accuracy. The FRS was borderline higher in the high-risk group (p = 0.04), in addition to patients with more extensive coronary artery disease (p = 0.001). However, the FRS had poor discrimination in detecting patients containing high-risk TCFA (area under the curve of 0.55). Adding angiography slightly improved the area under the curve to 0.64. The authors concluded that clinical and angiographic characteristics had poor predictive accuracy in identifying patients with untreated high-risk plaques responsible for future coronary events. The absence of a direct link between clinical factors and the presence of high-risk, nonculprit TCFA responsible for future MACE underscores the less-than-optimal risk stratification currently used in clinic practice. It also highlights the unique role that intracoronary imaging has to properly identify high-risk, nonculprit TCFA in patients with ACS.

**Applying the FRS to Predict High-Risk TCFA Detected by IVUS in Patients With ACS**

Although an attractive concept, a number of reasons might explain the lack of predictive ability of an aggregate FRS + angiographic approach in this study. It is important to note that the Framingham criteria may not be appropriate for the kind of relational analysis in this paper, when dealing in patients with documented ACS events. Originally conceived in 1948, at a time when CAD was not well understood, the FRS has been successively improved to predict long-term cardiovascular risk (12,13). However, this prediction algorithm was developed and validated exclusively in patients without overt cardiovascular disease, and should be applied only in the setting of primary prevention.

Second, nonculprit-related MACE after ACS was previously estimated at a rate of 6% to 7% per year (14,15). However, the PROSPECT study identified a much lower event rate, which was close to 3% to 4% per year (6). This lower event rate, even though not the primary focus of this study, could make it difficult to identify clinically relevant, independent predictors. More importantly, the majority were “soft events,” including recurrent angina, hospitalization, and repeat revascularization. The FRS was not designed to predict soft events in patients with established cardiovascular disease, after ACS. Furthermore, even if it did correlate to high-risk plaque, one cannot be sure what would be the value of FRS predicting high-risk plaque if it did not reliably predict events in this population. Even in the original PROSPECT dataset, TCFA morphology by itself was associated with few events. It was necessary to add 2 additional predictors, including plaque burden and minimal luminal area, to achieve clinical relevance. Plaques with ≥2 predictors had between 4% to 6% MACE per year (6). In addition, the incidence of this “high-risk TCFA” (16) was present in only 4.6% of the population, as previously reported in the Motoyama et al. study (9). Therefore, applying a marker of hard events such as FRS would not perform well if the predominant event of interest was anatomic, or is not very common, and even if clinical, is a soft one, such as rehospitalization for ACS or revascularization.

The PROSPECT study established the natural history of high-risk, nonobstructive TCFA. However, it was not designed to test the role of optimal medical therapy in reducing events. It is possible that a very aggressive pharmacological protocol guided towards plaque regression may have obtained even lower event rates. In fact, current studies conducted to evaluate the role of lifestyle modifications and aggressive medical therapy documented significant reductions in MACE after ACS (17), suggesting a consistent response at the plaque level.

**Susceptibility of High-Risk TCFA to Plaque Regression**

Novel coronary imaging, not only contributed to identify the incidence, morphological predictors, and the natural history of high-risk TCFA, but also documented consistent changes in plaque...
composition after aggressive statin therapy. Pivotal, sequential, noninvasive studies evaluating high-risk, low-attenuated plaques documented significant reductions in plaque volume after 1 year of aggressive statin therapy (18). Simultaneously, IVUS virtual reductions in plaque volume after 1 year of aggressive therapy (19). Optical coherence tomography studies complemented these findings, with improvements of fibrous cap thickness after pitavastatin therapy (20). More recently, the YELLOW (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy) trial identified patients with lipid-rich, nonculprit plaques, using near-infrared spectroscopy. Lipid content, as quantified by lipid core burden index, showed significant reduction in patients randomized to 40 mg of rosuvastatin after 7 weeks of therapy (21). Therefore, high-risk TCFA is highly responsive to aggressive medical therapy. However, medical therapy must be appropriately given, and changes in lipid profile must be documented as improvements in the demographic profile.

Documentation of high-risk, nonculprit lesions is only relevant if they lead to recurrent events. These events occur mainly because of lack of aggressiveness in secondary prevention, or TCFA refractoriness to medical therapy. Extensive neovascularization, intraplaque hemorrhage, and rapid expansion may play a role in refractoriness, leading to recurrent events. However, this is the exception and not the rule. The majority of ruptured plaques will heal without consequences. Furthermore, optimal medical therapy has proven to stabilize plaques and reduce events. In this study, baseline demographic predictors at the time of intervention failed to establish a link between clinical factors and nonculprit TCFA in patients with ACS. Thus, a 1-time “look” correlating FRS or demographics to presence of a high-risk plaque at another single time point may not be enough.

Failure to establish a direct link between the FRS and high-risk TCFA may not necessarily exclude the possibility that clinical and angiographic characteristics may have predictive accuracy in identifying patients with untreated high-risk plaques related to future adverse events. Clearly, more research is needed to reach this conclusion. Furthermore, the potential value of comprehensive 3-vessel imaging assessment (either invasive or noninvasive) to assess plaque phenotype must be linked to hard events before it can be recommended for clinical use. Such comprehensive evaluation, especially if it is invasive, has not led to a major change in therapy at this time, and it may itself trigger harmful complications.

To properly test predictability of clinical factors for recurrent events, the design must include sequential analyses of these factors, including low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood pressure, glycosylated hemoglobin, and physical activity. Considering the beneficial effects of aggressive statin therapy at the plaque level (22), large delta changes will certainly reduce the incidence of high-risk, nonculprit TCFA, and prevent MACE. Conversely, small or negative delta changes will increase incidence, and probably predict MACE. Therefore, it is premature to say that demographic factors are not associated with clinically relevant, high-risk, nonobstructive TCFA after ACS. Additional studies are urgently needed to completely elucidate this issue.

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