The PROSPECT Study

Principal Investigator Gregg W. Stone, MD, FACC, FSCAI, from Columbia University Medical Center/New York-Presbyterian Hospital, shares his insight on the impact and potential of imaging modalities used to predict vulnerable plaque.

On January 20, 2011, Gregg W. Stone, MD, FACC, FSCAI, et al published in the *New England Journal of Medicine* findings from PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), a prospective natural history study of coronary atherosclerosis (2011;364:226–235). *Cardiac Interventions Today* interviewed Dr. Stone to find out his expert opinion on this study.

What effect do you think these data will have, and do you believe that lesion-specific percutaneous coronary intervention (PCI) will be performed in the future?

These data are very important to guide future studies and therapies. PROSPECT is the first prospective, natural history study of atherosclerosis that sought to determine whether we can predict which lesions are likely to cause future adverse cardiovascular events for patients. PROSPECT tells us that we can predict and identify so-called vulnerable plaques, that is, lesions that place patients at risk for future adverse events.

Specifically, we found that clinical information and angiographic data were not sufficient to predict which lesions would cause future events, but we were able to use a combination of grayscale and radiofrequency intravascular ultrasound (IVUS) data, also known as *virtual histology*, to identify three characteristics of lesions that are high risk (high plaque burden, small minimal luminal area, and lesions identified by virtual histology as being thin-cap fibroatheromas). Together, those three variables in a multivariable model were quite accurate in predicting future events with a C statistic of 0.82 to 0.84.

We do not have data yet to suggest PCI is warranted in such lesions. PCI itself can lead to periprocedural complications as well as restenosis or stent thrombosis. Thus, a randomized trial is necessary to determine whether the benefits of treating borderline and nonischemia-producing lesions are greater than the risks.

Do you believe that PROSPECT will help us improve preventive medicine, both systemic and PCI based?

I hope the answer is yes. First of all, it brings attention to this major health care issue. It also advances our knowledge in showing us that it is not mild, insignificant lesions that cause future adverse cardiovascular events, but the substrate actually is, in most cases, severe plaque and severe metabolically active, inflamed plaque with a large necrotic core and a thin, fibrous cap—so-called thin-cap fibroatheromas.

We need to be able to (1) identify those patients and (2) be able to develop and target specific pharmacologic and potential device-based strategies for these patients. This is really just the start of our long journey—not the end.

Are there any other imaging modalities in addition to virtual histology that can predict lesion risk?

There are several other imaging modalities that have been developed for this purpose, from noninvasive modalities, such as computed tomography (CT) scanning, magnetic resonance imaging, and positron emission tomography scanning (each with or without specific targeted contrast media or labeled antibodies), to other invasive modalities. With regard to the latter, there have been at least a dozen catheters that have been developed to try to identify either specific anatomic, chemical, or functional characteristics of vulnerable plaque.

Two modalities other than virtual histology that have received the most interest have been optical coherence tomography and near-infrared spectroscopy. Both of these modalities have advantages and disadvantages compared to virtual histology, but neither has yet been validated in a natural history study the way radiofrequency IVUS has been. Thus, it is currently unknown whether other modalities can predict lesions that are at risk for future events, although it is possible that they may be able to. Likewise, it is also unknown whether those modalities can predict such lesions with more accuracy, with similar accuracy, or with less accuracy than radiofrequency IVUS.

Do you think that dual-antiplatelet therapy contributed to the low rate of myocardial infarction events?

I do. I think that not just dual-antiplatelet therapy but the intensive pharmacotherapy and close clinical follow-up of the patients in this trial clearly contributed to their favorable prognosis. The rate of death and myocardial infarction was relatively low in the trial, although the overall event rate of 20% in the study over a 3-year

median follow-up was not dissimilar to what was seen years ago from the PROVE-IT TIMI 22 study.

This suggests that the intensive pharmacotherapy and close follow-up converted potential myocardial infarctions to unstable angina, which were then successfully treated with PCI. Many of the patients did have clear plaque rupture and plaque progression during follow-up, but they were able to maintain some flow in the coronary vessels, such that they would present with more than unstable ischemic syndromes but not with an acute infarct or with sudden death.

What would be your advice for high-risk patients with unknown coronary artery disease, and the two-thirds of all patients with sudden cardiac death?

The most important implications of PROSPECT may relate to the potential identification of those patients and lesions at risk in the general population. There are three-quarters of a million or more myocardial infarctions and sudden cardiac deaths per year in the United States, and the majority of these patients don't even know they have coronary artery disease, let alone vulnerable plaque.

If we can use the types of principles that we identified in the PROSPECT study to identify those patients, then we may be able to develop more intensive pharmacologic and/or revascularization strategies to prevent death and myocardial infarction in the general populace.

What additional studies need to be undertaken going forward?

First, we should perform studies with the other imaging modalities, both noninvasive and invasive, to determine their clinical utility in identifying lesions and patients at risk. Second, we need therapeutic strategy studies for lesions at risk. Third, I think most important at this point is large population screening studies using noninvasive modalities with the techniques that, at least right now, best approximate the information we get from virtual histology IVUS (eg, multislice CT). Such studies would allow us to determine whether identification of high-risk lesions is possible in patients in whom, at a minimum, we would consider intensive pharmacotherapy with statins and aspirin.

What concerns, if any, should be elucidated about the PROSPECT study?

One concern would be that the technique that we used in the study, three-vessel IVUS, was not without complications; there was a 1.6% major complication rate, most of which were coronary dissections. But a few patients had myocardial infarctions from the imaging in the study, and it was a very aggressive imaging protocol that we incorporated.

I think that rate can be reduced by being less aggressive when the catheter is passed across lesions and by improvements in catheter technology in the future. Nonetheless, there will always be some risk to invasive screening.

As of now, we do not recommend three-vessel screening to look for vulnerable plaques, in particular because we do not have a therapy that has been proven to be beneficial once discovered.

Another concern is that we have not compared radiofrequency IVUS to the other modalities, such as optical coherence tomography and near-infrared spectroscopy. We don't know whether these other modalities would have similar utility or lesser or more utility than radiofrequency IVUS.

What needs to happen next from a technology standpoint?

Obviously, the catheters need to improve; they can always improve. Signal-to-noise ratio can increase. Noninvasive imaging has a long way to go to be able to have the same fidelity and freedom from motion and other artifacts that the invasive, intravascular catheters have. Technical improvements of the imaging modalities will further increase the positive and negative predictive value of these tests.

What are your take-home points about the PROSPECT study?

This trial was a true labor of love. It took about 8 to 10 years from conception to completion. It required the development of novel and proprietary methodology to be able to analyze every single millimeter of the coronary tree with angiography, with grayscale IVUS, and with radiofrequency IVUS. A subset of the patients had palpography, a novel technique to measure stress and strain; a subset underwent multidetector CT. Palpography did not prove to be predictive from the subset of patients that we enrolled, which was an important negative, but radiofrequency IVUS was strongly predictive. A huge amount of imaging information and statistical analyses were required to derive these results, which we hope have advanced our understanding of the natural history of atherosclerosis and the vulnerable plaques that place patients at risk for future adverse cardiovascular events. ■

Gregg W. Stone, MD, FACC, FSCAI, is Professor of Medicine and Director of Cardiovascular Research and Education of the Center for Interventional Vascular Therapies at Columbia University Medical Center/New York-Presbyterian Hospital, and is Codirector of the Medical Research and Education Division at the Cardiovascular Research Foundation in New York. He has disclosed that he is a paid consultant to Volcano Corporation and InfraReDx, Inc. Dr. Stone may be reached at (646) 434-4134; gs2184@columbia.edu.