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EDITORIAL COMMENT

Vulnerable Plaque and Einstein's Definition of Insanity*

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A quote often attributed to Albert Einstein defines insanity as "doing the same thing over and over again and expecting different results." That's exactly what has happened with efforts to identify the elusive entity of "vulnerable plaque" using various coronary imaging modalities. Proponents of this concept have tried for decades to demonstrate the existence of a specific plaque phenotype that portends major adverse outcomes, such as myocardial infarction or sudden cardiac death. In many cases, an underlying motivation for identifying vulnerable plaques is the notion that interventional cardiologists could place a stent within such plaques, thereby avoiding untoward outcomes. Now, after a long series of failures, it seems abundantly clear that the entire concept of vulnerable plaque is fundamentally flawed and reflects an overly simplistic view of the pathophysiology underlying coronary events.

The concept of vulnerable plaque was first proposed by Muller et al. (1) in 1994. Then, in 1999, investigators based in Greece placed intracoronary catheters containing a highly accurate thermistor to measure the temperature of the vessel wall (2). They reported that patients with normal coronaries showed uniform temperature, but that patients with unstable angina or acute myocardial infarction had significant "temperature heterogeneity" within culprit lesions. This research was met with an explosion of interest in finding so-called "hot" plaques. In a frenzy of activity, companies were formed, inviting investors to fund efforts to develop coronary thermography as the next big thing. A flurry of papers, mostly low-quality, uncontrolled studies, confirmed the presence of abnormal temperature readings in the coronary arteries of patients with unstable syndromes. Then, almost inexplicably, silence.

The rise and fall of coronary thermography is emblematic of a pattern that has recurred repeatedly during the last 2 decades. The list of failed techniques for vulnerable plaque detection seems almost endless: thermography, intravascular ultrasound (IVUS) virtual histology, optical coherence tomography, angioscopy, intravascular magnetic resonance, near-infrared spectroscopy (NIRS), intravascular elastography-palpography, multidetector computed tomography, and positron emission tomography. In each case, a technique for vulnerable plaque detection is developed, promoted, and widely hailed as a breakthrough, followed by "confirmation" via uncontrolled observational studies or registries. Yet, none of these methods have been properly validated via well-designed randomized controlled studies, and none have achieved routine clinical use.

The entire field is seemingly plagued by the vexing problem of negative publication bias. When a promising new diagnostic method is reported, additional studies are performed, but only the "positive" studies are reported. Negative studies end up in a file drawer. The resulting enthusiasm typically leads to overly optimistic expectations and occasionally clinical application by enthusiastic practitioners. Unfortunately, the under-reporting of negative studies has not been eliminated following the development of mandatory registries such as ClinicalTrials.gov. As a consequence, it can take years before the limitations emerge for each proposed vulnerable plaque imaging modality. Many years ago, during the thermography craze, I watched in horror at a live course while an interventional cardiologist measured plaque temperature, then placed a stent in a nonsignificant stenosis to "prevent" a future coronary event.

In this issue of the *Journal*, Yamamoto et al. (3) followed the patterns observed for many previous

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vulnerable plaque imaging studies. The authors used NIRS in the multicenter COLOR (Chemometric Observations of Lipid Core Plaques of Interest in Native Coronary Arteries Registry) to study nearly 2,000 patients undergoing coronary angiography with

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possible coronary intervention. The primary variable of interest was "lipid rich plaque." The study completed 4 years ago, but appears to have resided in a file drawer since early 2016. The study was large, but not randomized, and the primary hypothesis was vaguely written: "Identify associations of LCP [lipid core plaque] with angiographic or symptomatic presentation of coronary artery disease in a catheterization laboratory population" (4). The results were not favorable. There was no relationship between lipid rich plaque and clinical outcome, and the imaging procedure itself was associated with some harm: a catheter-related complication rate of 0.5% in a population with a culprit lesion event rate of 8.3%. Essentially, for every 16 patients with a spontaneous adverse clinical outcome, 1 experienced a complication from the procedure. In parallel, a more favorable study, also not a randomized controlled trial (RCT), was submitted and published within 1 year of completion. (5)

Like many prior studies of vulnerable plaque imaging, there were important flaws in the design and conduct of the current study. Interventional operators were not blinded to the findings obtained via the NIRS imaging system. Accordingly, the individual collecting the imaging data was free to alter the interventional procedure based on the NIRS imaging findings. This lack of methodological rigor has plagued the field of vulnerable plaque imaging in virtually all prior studies. Amazingly, the widely cited IVUS virtual histology study, PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), offered broad and unsupportable conclusions based on a total of 1 cardiovascular death and 14 myocardial infarctions at culprit lesions (6). All of the rest of the observed adverse outcomes in PROSPECT were "soft" events, such as hospitalization for unstable angina or revascularization.

Why have so many efforts to identify vulnerable plaque failed to yield a useful imaging modality for this clinical application? The principal problem is the focus of these efforts on individual plaques. Although it is true that most coronary events occur at a single site, atherosclerosis is a systemic disease, not a focal process. IVUS imaging in atherosclerosis regression-progression studies reveals the presence of plaque at nearly every coronary site in long motorized pullbacks (7). Accordingly, to successfully predict outcome, an imaging modality would need to examine every millimeter of all major coronary arteries. Intracoronary imaging methods cannot safely examine all coronaries throughout their lengths. Although noninvasive modalities such as coronary computed tomography can image the entire coronary tree, these approaches lack the spatial and temporal resolution to adequately characterize coronary plaques. Furthermore, coronary disease is a dynamic process, but nearly all prior efforts to identify vulnerable plaque have imaged vessels at a single point in time. Coronary plaques are constantly evolving through processes such a plaque hemorrhage, erosion, or rupture without obvious clinical consequences. Even if an imaging modality could identify a high-risk plaque, we know from studies of coronary intervention that placement of a stent in such a plaque is unlikely to reduce subsequent morbidity and mortality (8).

The occurrence of an acute coronary event is related to many systemic factors that are not directly related to individual plaques. For example, platelet activity plays a key role in acute coronary thrombosis, and platelet-related biomarkers such as CD40 ligand are strongly associated with acute coronary events. Systemic inflammation is also a well-documented factor associated with acute events. A significant fraction of patients experience a myocardial infarction with angiographically normal coronaries. Accordingly, the concept of a specific vulnerable plaque waiting to rupture is too simplistic. In fact, the therapies that have been demonstrated to reduce coronary events are all systemic, such as lipid-lowering therapy, antiplatelet drugs, antithrombotic agents, and anti-inflammatory therapies.

What should we expect from future studies of proposed imaging methods to detect vulnerable plaque? We live in an era where improvements in outcomes are essential to the acceptance of new diagnostic and therapeutic interventions. Accordingly, an imaging modality design to detect vulnerable plaque must eventually lead to a properly blinded, prospective RCT with well-defined, prespecified morbidity and mortality outcomes. The use of treatment strategies guided by the proposed imaging method must show that imaging results in a clinically meaningful benefit on morbidity-mortality outcomes. To date, proponents of vulnerable plaque imaging have not conducted high-quality trials, and no imaging modality has demonstrated a meaningful clinical benefit. Although definitive RCTs are large and complex, they are essential to provide the

medical community with the necessary evidence of a useful clinical benefit for plaque imaging. After thousands of vulnerable plaque papers and more than 2 decades of research, we have little to show for these efforts.

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