Coronary stents are an essential tool in the percutaneous treatment of obstructive coronary artery disease. Coronary stents, particularly drug-eluting stents (DES), reduce angina in stable patients and reduce myocardial infarction or death in patients with acute coronary syndromes. However, even the current best-in-class second-generation DES remain at risk of developing stent restenosis or stent thrombosis, complications that cause myocardial ischemia, myocardial infarction, or even sudden cardiac death.1 More worrisome is that even extended dual antiplatelet therapy does not eliminate the risk of stent thrombosis.2

See Article by Madder et al

Neatherosclerosis, the formation of an atherosclerotic-type plaque overlying an implanted stent, is an emerging complication of coronary stents that may underlie stent thrombosis and restenosis.3,4 Initially characterized by foamy macrophage infiltration, neoatheroma may mature and develop necrotic cores. Such cores may evolve with or without a thin fibrous cap or calcification. Neoatheroma with thin fibrous caps can undergo plaque rupture and cause an acute coronary syndrome. Autopsy studies reveal that neoatherosclerosis exists in ≥20% of coronary stents.5 Neoatherosclerosis is 2× to 3× more prevalent in DES compared with bare metal stents, and occurs similarly in first- and second-generation DES. It is hypothesized that in absent or dysfunctional endothelium induced by drugs or polymers the DES might promote the formation of neoatherosclerosis. It remains of considerable interest to ascertain if biodegradable polymers or stents will reduce the incidence of neoatherosclerosis.

Imaging is necessary to diagnose coronary neoatherosclerosis in living patients. Intravascular optical coherence tomography (OCT), intravascular ultrasound (IVUS)-virtual histology, and angioscopy are approaches that demonstrate the potential to detect coronary neoatherosclerosis.6,7 OCT offers superb spatial resolution, and it is the most frequently used approach for imaging neoatherosclerosis. One study of patients with late stent thrombosis demonstrated OCT neoatherosclerosis in ≥70% of cases.8 Clinical associates of OCT-detected neoatherosclerosis include stents >4 years old, DES, active smoking, chronic renal insufficiency, and the absence of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockade.9

Intravascular near-infrared spectroscopy (NIRS) is a catheter-based coronary imaging method that illuminates tissues with near-infrared light with wavelengths from 780 to 2500 nm.10 After interacting with absorbing and scattering tissue or blood, reflected NIR light is detected by the catheter. Plaque cholesterol moieties such as cholesteryl oleate, free cholesterol, and cholesteryl linoleate may be detected by analyzing the intensity of the return NIR light over a range of wavelengths (diffuse reflectance spectroscopy). NIRS is combined with IVUS in a single catheter for simultaneous chemical-structural imaging, and the NIRS information can be displayed on a 2-dimensional angular and longitudinal map (chemogram). As with other reflectance-based light techniques, depth information cannot be resolved (there is no axial resolution). Most of the NIRS signal is reported to be collected from the first 1 mm of tissue away from the catheter, and the NIRS signal is surface weighted. NIRS can provide a semiquantitative measure of lipid burden (so-called lipid-core burden index). NIRS is Food and Drug Administration approved for the detection of lipid-core plaques, and it is under active investigation for the detection of vulnerable plaques11 and plaques at risk of periprocedural myocardial infarction.12 To date, however, limited information on NIRS’ ability to detect neoatherosclerosis is available.

In this issue of Circulation: Cardiovascular Imaging, Madder et al13 investigated the ability of NIRS–IVUS to detect coronary stent neoatherosclerosis. In this study, 41 of 309 patients undergoing coronary NIRS–IVUS as part of a registry harbored a pre-existing stent (>4 months old). A total of 60 pre-existing stents (average 5.5 years postimplant, 83% DES, with half second-generation DES) were successfully imaged with NIRS–IVUS. These 60 stents were compared with 60 freshly implanted stents undergoing NIRS–IVUS, matched for clinical indication, age, and sex. Of note, NIRS–IVUS images were interpreted off-line, which limits the point-of-care applicability of this approach.

The NIRS analyses were intriguing. NIRS identified a lipid-rich plaque in one third of pre-existing stents. In addition, one sixth of pre-existing stents exhibited a large lipid-core plaque, defined by a max lipid-core burden index ≥400. However, as acknowledged by the authors, NIRS, a method without axial depth resolution, cannot resolve whether a lipid signal arises from neointima overlying the stent, or from a plaque deep to the stent, or both. This lack of axial (depth)
resolution capability limits NIRS detection of neatherosclerosis. The authors attempted to address this limitation by classifying stents into 1 of 3 patterns based on the IVUS findings: pattern I, stents without neointimal tissue (this pattern is not be relevant to neatherosclerosis); pattern II, stents with evidence of neointima and plaque (not possible for NIRS to resolve where a lipid signal may arise from); and pattern III, stents with neointima that obscured stents struts at the site of lipid-rich plaque or neointima that were immediately adjacent to the underlying media (no plaque). Pattern III with a positive NIRS signal might reflect neatherosclerosis because confounding plaque is presumably too deep to contribute to the NIRS signal, or is absent. However, without histopathologic validation, or at least concomitant imaging with OCT, it remains unclear if NIRS–IVUS pattern III accurately identifies neatherosclerosis.

Despite these limitations, this NIRS–IVUS stent classification pattern identified stents that subsequently developed stent failure (restenosis or thrombosis). Patients with NIRS–IVUS pattern type II or type III developed stent failure in 4 of 13 stents (31%), whereas patients with NIRS–IVUS type I pattern developed a stent failure in only 1 of 47 stents (2%, \(P<0.05\)). With the caveat of small numbers, this is a provocative finding worthy of further study.

In summary, Maddern et al\(^1\) are to be congratulated for investigating the ability of NIRS–IVUS to shed light on the pathogenesis of neatherosclerosis, an emerging indicator of high-risk stents at risk of stent thrombosis and restenosis. In addition to OCT, IVUS-virtual histology, angiography, and possibly NIRS-IVUS, novel imaging approaches such as intravascular photoacoustic tomography\(^{2,3}\) and near-infrared fluorescence molecular imaging\(^{16,17}\) might prove useful in detecting neatherosclerosis. We have much to learn about this disease and how to prevent it—and intravascular imaging remains essential in this endeavor.

Disclosures

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References

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