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EDITORIAL COMMENT

Long Lesions, Hard Endpoints, and Intravascular Ultrasound*

Harold L. Dauerman, MD

In this issue of *JACC: Cardiovascular Interventions*, Shin et al. (1) present a meta-analysis comparing the efficacy of intravascular ultrasound (IVUS) versus angiographic guidance for coronary stent placement. The abundance of meta-analyses (2–4) on this topic is a tribute to the 20-year history of this debate. The present meta-analysis demonstrates a 66% reduction in major adverse cardiovascular events (MACEs) with IVUS versus angiographic guidance among patients undergoing high-risk percutaneous coronary intervention (PCI) with second-generation drug-eluting stents. The 2011 American College of Cardiology guidelines for PCI weakly endorsed the use of IVUS in PCI guidance: "IVUS may be considered for guidance of coronary stent implantation, particularly in cases of left main coronary stenting (Class IIB, Level of Evidence: B)" (5). On the basis of the present meta-analysis, should the guidelines change and recommend routine IVUS guidance for high-risk PCI?

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IN PURSUIT OF HARD ENDPOINTS

IVUS-guided PCI has spanned 2 decades, including balloon angioplasty optimization, bare-metal stent apposition, and now second-generation drug-eluting stent trials (6–8). IVUS-guided PCI is successful in achieving the anatomic goal of more aggressive balloon dilation and improved final luminal diameters (9,10). Other IVUS trials go further to suggest a reduction in target lesion revascularization (TLR) with IVUS as opposed to angiographic guidance (6). The present meta-analysis includes 3 randomized trials involving only second-generation drug-eluting stents and complex coronary intervention (6–8). The investigators have a firmer purpose than stated in the individual trials: can IVUS guidance prevent heart attacks and cardiac death? They pose this as follows: "However, the reduction in MACEs was driven mainly by the reduction in TLR, without between-group differences in cardiac death or myocardial infarction, which may be more clinically important events."

Using the hard MACE endpoint of cardiac death, myocardial infarction, or stent thrombosis, the present meta-analysis demonstrates a significant reduction in hard MACEs with IVUS guidance of high-risk PCI (1.2% vs. 0.4%; $p = 0.04$). These results should be compared with those of a recent IVUS-guided PCI meta-analysis: a softer MACE event definition (which includes TLR) shows event rates 5 to 10 times higher but similarly favors IVUS guidance (6.5% vs. 10.3%; $p < 0.0001$) (2). The wide range of MACEs depends primarily on what the trialists consider important: TLR, periprocedural myocardial infarction, stent thrombosis, or death?

The pursuit of the hardest endpoint has a goal: if clinicians are not adopting a new technology or pharmacology, do a large registry analysis or lump together many trials and try to show clinicians that this lack of adoption is costing lives. The lack of adoption of routine IVUS is not borne purely of laziness; excellent outcomes achieved without IVUS guidance damper enthusiasm for technology and pharmacology that may be seen as expensive or time consuming. For example, the largest of the 3 trials in the present meta-analysis is the IVUS-XPL (Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions) trial (6). The outcomes of angiography-guided second-generation

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From the University of Vermont College of Medicine, Burlington, Vermont. Dr. Dauerman is a consultant for and has received research grants from Boston Scientific and Medtronic.

drug-eluting stent placement in high-risk PCI are quite good: at 1-year follow-up, angiographic guidance led to a 0.3% rate of stent thrombosis and a 5.0% rate of TLR. Clinicians may ask whether the time and expense of routine IVUS is justified to drive the singular endpoint of TLR from 5.0% to 2.5% (with no impact on death, stent thrombosis, or myocardial infarction).

By grouping together 3 similar trials, the investigators drive the discussion toward a patient-oriented benefit that goes beyond repeat PCI: death, heart attack, and stent clotting are clearly bad enough to warrant the time required for intracoronary imaging. But the interventional cardiology community has a long history of limited adoption of all decision aids that are additional to angiography: coronary physiology, intracoronary imaging, and risk-scoring systems are easily available and infrequently used (11). Thus, resorting to meta-analysis to make a strong point may not sway physicians the way a single, adequately powered randomized trial would.

LONG LESIONS AND HIGH-RISK PCI

The key to broader adoption of IVUS-guided PCI may be 2-fold: 1) convincing clinicians that they are saving lives (or at least preventing stent thrombosis); and 2) demonstrating benefit in the context of an angiographic control group that has a truly high event rate. Unfortunately, the meta-analysis of Shin et al. (1) may not meet this clinical challenge. The strengths of their analysis are 4-fold: 1) focus only on patient-level data from 3 randomized clinical trials, with no inherently confounded registry data; 2) enroll only patients with high-risk coronary anatomy as defined by long lesions or chronic total occlusions; 3) include only patients treated with the best current technology; and 4) demonstrate benefit of IVUS guidance for a hard endpoint that is closer to a mortality benefit.

But 1 of their strengths turns out to be a weakness: enrollment of high-risk patients. There was a time when PCI of long lesions was clearly associated with an increased risk for stent thrombosis and restenosis (12). IVUS-XPL appropriately focused on patients receiving XIENCE stents of long length (≥28 mm) for long lesions (mean lesion length 39.3 ± 12.7 mm). Despite including 1,400 patients with long lesions, there was only 1 myocardial infarction at 12-month follow-up in the entire randomized trial. Furthermore, only 4 patients had stent thrombosis at any time in the first year, a 0.3% event rate in both the IVUS and angiographic groups. In the entire trial, the TLR rate was 3.5% (with a 50% reduction in TLR with IVUS vs. angiographic guidance, $p = 0.02$). Of note, the low event rate of this trial is not due to an entirely benign population of patients: one-third had diabetes mellitus, one-quarter were currently smoking, and one-half of the patients had acute coronary syndromes. These results emphasize an unintended conclusion from this randomized clinical trial: long lesions do not drive up event rates, and long lesions no longer define high-risk PCI.

Thus, it is not the investigators' fault that they end up with a weak p value of 0.04 for a meta-analysis focusing on a convincing hard endpoint: when you base a meta-analysis primarily on a single trial that shows outcomes that are the very definition of low-risk PCI, any benefit of new technology, imaging, or pharmacology becomes statistically risky. The weakness of IVUS's superiority in this meta-analysis is easy to see with a bit of imagination: if 1 patient ruptured a plaque in the IVUS-guided group leading to chest pain with elevated biomarkers 6 months after PCI, the 1-year myocardial infarction rate in the meta-analysis would have increased from zero to the still incredibly low rate of 0.09% (1 in 1,170). This single event, though, would have rendered the entire meta-analysis negative (0.5% vs. 1.2% hard endpoint rate, $p = 0.11$ by Fisher exact test).

THE FUTURE OF IVUS GUIDANCE

Intracoronary imaging has always played a vital role in the world of coronary intervention: as a research tool providing insights into plaque composition and as a clinical tool for lowering the risk for adverse events after stenting (13). Shin et al. (1) sought to provide clinicians with a simple algorithm regarding IVUS guidance: if you are putting a stent in a high-risk lesion, do IVUS. Unfortunately, the argument is less than convincing because of the strikingly low event rates for the no longer high-risk lesions included in the meta-analysis.

It seems unlikely that the current data argue for a Class I recommendation for routine IVUS guidance in the increasingly undefined field of high-risk PCI. However, intracoronary imaging, both IVUS and optical coherence tomography (14), remain vital in selected situations. Is the left main stent appropriately sized in a diffusely diseased vessel? Is the stent thrombosis due to plaque rupture or inadequate stent expansion? Is there a real lesion at the ostium of the left anterior descending coronary artery? Maybe the present meta-analysis fails to identify what truly high-risk PCI is and what routine IVUS algorithm should be used. Given advances in stent technology, a

truly high-risk PCI group with an excessive stent thrombosis or TLR event rate may no longer exist. But the suggestion of potential improvement in hard outcomes combined with decades of clinical experience in difficult situations may be enough to rewrite the PCI guidelines strongly in favor of the selected use of intracoronary imaging. Maybe the following fits the spirit of the meta-analysis and the long hard road of convincing clinicians of the important role of intracoronary imaging: Class I, Level of Evidence: A— intracoronary imaging, either IVUS or optical coherence tomography, is a vital tool that should be available in all interventional cardiology programs, with operators who are proficient in application of these technologies in selected situations in which diagnosis or treatment strategy is unclear.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Harold L. Dauerman, University of Vermont Medical Center, Division of Cardiology, McClure 1, 111 Colchester Avenue, Burlington, Vermont 05401. E-mail: harold.dauerman@uvmhealth.org.

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