EDITORIAL COMMENT

Linking Drug-Eluting Stent Kinetics and Clinical Outcomes

Insights From Optical Coherence Tomography*

Brigitta C. Brott, MD

Birmingham, Alabama

Drug-eluting stent release kinetics matter. This is demonstrated by the study of Guagliumi et al. (1) in this issue of JACC: Cardiovascular Interventions, which provides a description of the vascular responses to the next generation Resolute zotarolimus-eluting (sustained release) stent (Medtronic, Minneapolis, Minnesota). Vascular responses to this Resolute stent are compared with those of the original Endeavor stent (Medtronic), which delivers a more rapid release of zotarolimus.

Optical coherence tomography (OCT) imaging demonstrates that the Resolute sustained zotarolimus release stent yields less neointimal proliferation but more uncovered stent struts compared with the stent with faster release kinetics. These OCT findings provide an explanation for the results of the RESOLUTE All-Comers trial. This paper demonstrates that OCT can yield early clues to the efficacy and safety of new drug-eluting stent platforms by providing both endothelialization and neointimal proliferation data.

Zotarolimus-Eluting Stent Technology

The original Endeavor stent uses a cobalt-chromium platform, and releases zotarolimus rapidly (ZES-FR, zotarolimus-eluting stent faster-release kinetics) from a phosphorylcholine coating. Less than 50% of the zotarolimus remains on the stent at 24 h, and <6% at 7 days (2). The ZES-FR stent has a lower restenosis rate compared with bare-metal stents (BMS) (3), and provides greater neointimal coverage compared with sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) (4,5). However, at 6-month follow-up, the Endeavor stent is less effective at preventing restenosis than SES and PES, although the restenosis difference with PES is less evident at longer-term follow-up (6–9).

The Resolute stent is the next generation of the Medtronic zotarolimus-eluting stent (ZES-SR, zotarolimus-eluting stent sustained-release kinetics). It is composed of the same cobalt-chromium stent platform coated with a durable polymer designed for more prolonged drug release. The Biolinx polymer is comprised of 3 components: a hydrophobic portion to serve as a reservoir for zotarolimus, a hydrophilic polymer to enhance vascular compatibility, and an additional hydrophilic polymer to provide the initial burst release and enhance biocompatibility (10,11). This polymer combination provides an initial burst release of drug followed by sustained release, with half of the drug eluted in the first week and continued drug release beyond 4 weeks (10). In animal models, this combination demonstrates less late lumen loss but similar biocompatibility to BMS and ZES-FR stents (2,11).

The RESOLUTE first-in-man registry (12) and the RESOLUTE All-Comers trial (13) provide safety and efficacy data for this newer zotarolimus-eluting stent. The RESOLUTE All-Comers trial randomized 2,292 patients to either ZES-SR or everolimus-eluting stents (EES). Sixty-six percent of the patients had at least 1 off-label criterion for stent placement (13). At 12 months, the Resolute ZES stent was not inferior to EES, with no difference in the primary endpoint of target lesion failure. There was an in-stent late lumen loss for ZES-SR of 0.27 ± 0.43 mm versus 0.19 ± 0.40 mm in the EES group (p = 0.08). Of note, the ZES-SR group had a higher rate of definite and probable stent thrombosis (1.6%) than the EES group (0.7%, p = 0.05) (13), but this did not translate into a significant difference in death or myocardial infarction at 12 months. The RESOLUTE All-Comers trial, therefore, demonstrated that the ZES-SR stent was comparable to EES in safety and effectiveness (13).

Neointimal Strut Coverage and Overlapping Stents

Stent thrombosis and the differences between drug-eluting stent platforms remains a significant clinical concern. Human autopsy studies reveal that incomplete healing as evidenced by uncovered stent struts is the most powerful histological predictor of late stent thrombosis (14). In particular, the odds ratio for the presence of thrombus in a stent is 9.0 (95% confidence interval: 3.5 to 22) for lesions having a ratio of more than 30% uncovered to total struts per section (14). Drug-eluting stents elicit differing vascular healing responses, particularly involving rates of endothelialization (4). In animal studies, these differences between stent types are especially pronounced in regions of overlap, with a range of delayed healing, fibrin deposition, and inflammation (15).

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From the Section of Interventional Cardiology, the University of Alabama at Birmingham, Birmingham, Alabama. Dr. Brott is a cofounder of Endomimetics, LLC.
The ODESSA (Optical coherence tomography for DES SAFety) trial sought to evaluate healing responses in patients receiving overlapping drug-eluting stents (16,17). This trial randomized 77 patients to overlapping SES, PES, ZES-FR, or BMS. Angiography, intravascular ultrasound, and OCT were performed. OCT imaging at 6-month follow-up demonstrated significant differences in the degree of stent coverage and strut malapposition between stent types, although there was no significant difference between the regions of overlap versus nonoverlap. SES and PES had higher rates of uncovered or malapposed struts compared with ZES-FR and BMS. In particular, ZES-FR demonstrated near complete stent strut coverage, whereas SES had 8.1 ± 11.2% uncovered/malapposed struts, and PES had 4.05 ± 10.3% (SES and PES in comparison with ZES-FR and BMS, p < 0.001).

The Current Study

The current paper by Guagliumi et al. (1) describes the OCT, angiographic, and intravascular ultrasound findings of 21 patients who received overlapping ZES-SR. These patients were compared with the 22 historical control patients from the ODESSA study who received ZES-FR overlapping stents. OCT assessment at 6 months demonstrated that ZES-SR had less neointimal thickness, more uncovered stent struts, and more frames with >30% uncovered struts, when compared with the historical control evaluation of ZES-FR from the ODESSA study. These findings are consistent with the expectation that the ZES-SR would perform similarly to other drug-eluting stents, as evidenced by similar outcomes to EES in the RESOLUTE All-Comers trial (13).

An important difference between the ZES-SR group and the historical control ZES-FR group is the incidence of diabetes, in that the ZES-FR group had a 50% incidence of diabetes compared with 14% in the ZES-SR group (p = 0.02). Differences in neointimal thickness and strut coverage have been found when comparing diabetic and nondiabetic patients receiving SES (18). The authors address this issue by comparing strut coverage and neointimal thickness between diabetes classification for each stent type. This analysis did not demonstrate differences in response between diabetic and nondiabetic patients.

This study and the original ODESSA trial focus also on regions of overlapping stents compared with nonoverlapping segments. The ODESSA study found greater neointimal volume obstruction at regions of overlap for SES, PES, and ZES-FR (16). Stent overlap was also associated with more uncovered/malapposed struts for SES and PES, but not for ZES-FR, which had a low frequency of uncovered/malapposed struts. Surprisingly, the analysis of ZES-SR demonstrated no difference in neointimal thickness between overlap versus nonoverlapping regions and no increase in frequency of uncovered/malapposed struts at the region of ZES-SR overlap.

This study demonstrates the impact drug-eluting stent release kinetics can have on neointimal proliferation and vascular healing. The quest continues for a therapy that both effectively inhibits restenosis and enhances healing. OCT can be used to provide early insights into clinical safety and efficacy as new stents are evaluated.

Reprint requests and correspondence: Dr. Brigitta C. Brott, Section of Interventional Cardiology, University of Alabama at Birmingham, 510 20th Street South, FOT 907, Birmingham, Alabama 35294. E-mail: bbrott@uab.edu.

REFERENCES


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