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EDITORIAL COMMENT

Differential Clinical Benefit With Contemporary Drug-Eluting Stents

Fact or Fancy?*

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The evolution of coronary stenting from bare metal to first- and second-generation drug-eluting stents (DES) has been accompanied by a progressive reduction in both the device-oriented composite endpoint of target lesion failure (TLF) (composite of cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularization [CI-TLR]) as well as stent thrombosis (ST), with the greatest differential between these devices occurring during the first year following deployment.[1] Beyond 1-year, clinical events occur at a more consistent 2% to 3% per year annualized rate regardless of device. Specific stent design iterations that impact device oriented composite endpoints (TLF, target vessel failure [TVF], composite of cardiac death target vessel myocardial infarction and clinically indicated target vessel revascularization]) most importantly include stent strut thickness.[2-4] Thinner struts heal more rapidly and completely, induce less injury/inflammation, and have less peri-strut shear stress disturbance.[5,6] Stent strut thickness and width (strut volume) become progressively more important in small (≤2.5-mm diameter) vessels whereas an inverse, exponential relationship exists between target vessel size and both abluminal strut surface area coverage (device footprint) as well as strut volume/vessel volume ratio which are associated with thrombogenicity.[7] Further, stent strut geometry influences both strut level shear stress distribution and the degree of strut embedment which impact the time course and extent of endothelial strut coverage, healing, and thrombogenicity.[8] Following the development of bioinert/biocompatible permanent polymers with second generation DES, further iteration(s) in polymer distribution (abluminal-only versus conformal) or time course for resorption (bioresorbable versus permanent) have not demonstrated clinical benefit despite theoretic appeal.[9] Finally, stent platform flexibility/conformability, which correlates inversely with fracture resistance on bench/preclinical testing and influences vessel geometric distortion, has not shown clinical benefit in randomized, controlled clinical trials (RCCTs) comparing stents with differing flexibility.[10,11] In this context, the study by Jeong et al[12], published in this issue of *JACC: Asia*, is of interest.[12] Using the multicenter Intelligent Research in Sight-DES Registry of all patients undergoing percutaneous coronary intervention (PCI) with DES in Korea, the investigators evaluated the relative safety and effectiveness of 5 distinct DES platforms to 12 months post-implantation in complex high-risk indicated procedure (CHIP) patients. The definition of CHIP required ≥1 clinical (age >75 years, diabetes mellitus, chronic renal disease, prior coronary bypass surgery, cerebral or peripheral artery disease, chronic lung disease, primary PCI for ST-segment elevated myocardial infarction, poor left ventricular function/hemodynamic instability [left ventricular ejection fraction <30% or clinical cardiogenic shock]) plus ≥1 angiographic criteria (multivessel disease, severely calcified target lesions, diffuse long lesion [total stent length >40 mm] or target lesions involving a bifurcation, unprotected left main, or chronic total occlusion). Variables reflecting procedure complexity (mechanical cardiac support and

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use of ablative technologies) were not included in the CHIP definition. The 6,645-patient CHIP study population included a high prevalence of diabetes mellitus, multivessel coronary disease, and biomarker positive acute coronary syndromes and a low prevalence of poor left ventricular function or severe lesion calcium. Importantly, "severe lesion calcification" is not clearly defined by angiographic or intravascular imaging and "multivessel disease" is not quantitatively measured. Neither target lesion complexity by American College of Cardiology/American Heart Association classification nor target vessel diameter is presented. The clinical performance of CoCr EES (Xience, Abbott Vascular); Resolute ZES (Onyx, Medtronic Inc); PtCr EES (Synergy, Boston Scientific); Ultrathin Strut SES (Orsiro, Biotronik), and bioresorbable polymer SES (Ultimaster, Terumo Corp) were compared in the CHIP population. Multiple limitations of this analysis include: 1) DES treatment allocation was not random; 2) individual DES sample sizes are limited and variable; 3) significant baseline differences are present between treatment groups involving variables which impact the primary endpoint of interest (TVF) including age, insulin-dependent diabetes mellitus, prior PCI/coronary bypass surgery, chronic kidney disease, clinical indication for PCI (stable ischemic heart disease versus acute coronary syndrome), total number of stents or total stent length/patient, and average stent diameter (despite statistical adjustment for disparities through propensity score matching and inverse probability of treatment weighting, confounding most likely persists and P values/confidence intervals (CIs) are not adjusted for multiple testing); and 4) follow-up is limited to 1 year. The investigators conclude that differential risks for TVF exist by DES type (lower for Ultimaster, Orsiro, and Onyx versus higher for Xience and Synergy) and that RCCTs are required to confirm this hypothesis-generating observation.

Does evidence support this observation? First, although the relationship between thinner stent struts and a lower rate of stent related adverse outcomes is apparent for Orsiro, the investigators might strengthen this observation and widen the disparity between DES by analyzing target vessels ≤2.5 mm diameter or by using the surrogate of stent diameter if vessel diameter estimates are not available. In the prespecified analysis of small (<2.5 mm) coronaries from the BIO-RESORT (Comparison of Biodegradable Polymer and Durable Polymer Drug-eluting Stents in an All Comers Population) RCCT, TLF, and CI-TLR through 3-year follow-up were significantly lower with the thinnest strut stent.[13] In the SCAAR (Swedish Coronary Angiography and Angioplasty Registry), CI-TLR was reduced by 25% through 2-year follow-up of the thinnest strut stent compared with all other contemporary DESs.[14] The relative clinical benefit of ultrathin (<70 μm) versus thin (70 to 100 μm) strut stents appears less marked across all vessel sizes (versus small vessels) and concern has been expressed regarding the radial strength of ultrathin stents in fibrocalcific disease.[4,15,16] Second, support for the potential benefit of strut geometry comes from the Bioresorbable Polymer ORSIRO Versus Durable Polymer RELOLUTE ONYX Stents (BIONYX) RCCT which observed a significant reduction in stent thrombosis to 1 year (hazard ratio: 0.112; 95% CI: 0.01 to 0.87; $P = 0.11$) following treatment with the thicker (81μm), but round strut, Onyx, compared with the thinner (60 μm), but square strut, Orsiro, with benefit extending to 2 years (hazard ratio: 0.38; 95% CI: 0.14 to 1.07; $P = 0.057$).[17] This observation is consistent with preclinical studies relating peri-strut shear stress abnormalities to strut geometry and suggests that geometry may, in part, mitigate differences in strut thickness.[8] Thus, the relative benefit of Orsiro and Onyx in the current study finds precedent bench and RCCT support. However, the relative benefit observed for Ultimaster may not be explained by either strut thickness (80 μm) or polymer distribution (abluminal only) and is confounded by small sample size. If this is true, Ultimaster benefit might be ascribed to unique polymer composition (gradient poly[DL-lactide]-ε-caprolactone) and time course for concurrent polymer resorption/drug delivery (3-4 months) which have been associated with more rapid endothelial coverage, greater endothelial barrier protein (vascular endothelial-cadherin) expression, and a favorable endothelial cell shape index.[18] Third, the definition of CHIP is broad and eclectic so that benefit derived from a specific DES type will likely reflect similar benefit in other subgroups within a large-scale RCCT. Thus, although several of the investigators' observations appear mechanistically plausible, verification by large-scale RCCT is required. Too often, stent iterations with theoretic appeal based on bench or observational clinical experience fail to produce the expected clinical benefit when evaluated in large-scale RCCT. As the

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investigators acknowledge, this analysis should be considered hypothesis-generating.

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