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EDITORIAL COMMENT

Newer-Generation Drug-Eluting Stents in Patients Undergoing Complex Percutaneous Coronary Intervention*

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Coronary anatomic complexity is frequently encountered in patients with severe obstructive coronary artery disease (CAD), which serves as a major determinant of decision making for the indication of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (1). The evolution of stent technology has led to significant benefits of the newer-generation drug-eluting stents (DES), providing improved clinical outcomes of patients undergoing DES implantation (2,3). On the other hand, over a 5-year follow-up of the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; NCT01471522) trial (4), there was no significant difference in event-free survival between the invasive strategy (invasive coronary angiography and revascularization if necessary) plus optimized medical therapy and conservative management with optimized medical therapy alone. This leads us to reconsider the management of and the indication for invasive procedures in patients with obstructive CAD.

DES are the most common stent type in current clinical practice and are designed to reduce the proliferation of neointimal tissue through prevention of the migration of smooth muscle cells, the main source of arterial collagen, into the neointima, but they also contribute to delayed endothelization (5). With the increased use of DES in complex PCI, some clinical trials have demonstrated that DES have limited ability to prevent target lesion revascularization in patients with complex lesions, although some reported similar outcomes between patients with complex PCI and those with noncomplex PCI (1,6,7). These observations have driven clinical studies that investigate the safety and efficacy of the newer-generation DES in complex PCI.

In this issue of *JACC: Asia*, Park et al (8) sought to investigate the differences in the clinical outcomes in patients treated with zotarolimus-eluting stents (ZES) (Resolute Integrity, Medtronic) according to lesion complexity with the use of data available from a multicenter prospective registry (the CONSTANT registry). The polymer used with the Resolute Integrity is BioLinx (Medtronic), which is designed to release zotarolimus from the surface of the stent followed by extended drug elution (approximately 85% of the zotarolimus is released by 60 days, completely by 180 days), enabling sustained drug release to control neointimal hyperplasia in coronary lesions. The stent strut of the Resolute Integrity is thinner (90 μm) than that of earlier-generation DES (100-150 μm), and its unique platform offers high transit performance and the flexibility to accommodate complex vascular geometries and lesion morphologies (9). The Park et al (8) study population consisted of a mixed cohort of 926 patients, including stable angina (n = 290), unstable angina (n = 239), non-ST-segment elevation myocardial infarction (n = 197), and ST-segment elevation myocardial infarction (n = 200). The investigators analyzed clinical outcomes including target lesion failure (TLF), cardiac death, target-lesion myocardial infarction, and target lesion revascularization in patients with and without complex PCI.

Although there is no universal definition, the concept of complex PCI involves clinical risk factors and characteristics of coronary lesion and PCI

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procedures. In this study by Park et al (8), a coronary lesion was considered to be complex if any of the following was identified: ≥3 lesions treated, 3 vessels treated, severe calcified lesions, bifurcated lesions with 2 stents implanted, left main disease, chronic total occlusive lesions, and diffuse long (total stent length ≥60 mm) lesion. In the complex PCI group, the 2-year risk of TLF was not significantly higher than in the noncomplex PCI group (complex PCI vs noncomplex PCI: 4.8% vs 3.7%; adjusted hazard ratio: 1.157; 95% confidence interval: 0.476-2.808; $P = 0.748$). The same trend was observed for all composites of the clinical outcomes.

Thus, the investigators found that the clinical outcomes were similar between the 2 groups categorized according to the lesion complexity up to 2 years after ZES implantation. A major strength of the study is that it is an analysis from pooled data that address an unselected patient population, including acute and chronic coronary syndrome, which would be representative of current clinical practice. Yet, careful consideration is required for interpretation of their observations. Because this study was not powered to assess clinical outcomes between complex and noncomplex lesions treated with PCI, further follow-up is warranted for the assessment of device-oriented adverse events, such as stent thrombosis (ST) (1.2% in the complex PCI group vs 0.4% in the noncomplex group; $P = 0.352$). Furthermore, owing to the nature of an observational study, medical therapies, including the duration of dual antiplatelet therapy (DAPT), an efficient strategy to prevent ST but contributing to increased risk of bleeding, were not exactly same for the 2 groups. In fact, DAPT therapy was prescribed for a minimum of 12 months after the index procedure, and they observed extension of the DAPT beyond 1 year in both the complex and the noncomplex PCI groups (85.7% vs 80.7%, respectively; $P = 0.097$). This may be a potential confounding factor for event rates of the 2 groups, especially for ST as well as major bleeding.

Although follow-up coronary angiography was performed at 9 months after the index procedure according to clinician decision, coronary angiography alone could not detect unfavorable in-stent vascular tissue response after DES implantation. In the index procedure in acute coronary syndromes, presence of thrombus in the culprit lesion may lead to stent malposition and underexpansion of the implanted DES, contributing to worse clinical outcome (10). A study using optical coherence tomography has shown that post-stent morphologic features, such as irregular protrusion and small minimal stent area, are independent predictors of worse clinical outcomes (11). Detailed evaluation with the use of new intracoronary imaging modalities may help to elucidate mechanisms of stent failure in patients undergoing complex PCI with DES (5,12,13).

In this study (8), the use of intravascular imaging guidance was 43% (44.1% in complex PCI and 42.9% in noncomplex PCI), which is relatively higher than in the United States and Europe (10). Although that may explain the similar outcomes between complex and noncomplex PCI, long-term follow-up data for more than 2 years remain to be elucidated in further studies. Moreover, this study was an analysis from pooled data in which Resolute Integrity was used for PCI, limiting generalizability in the contemporary clinical practice of increasing use of more recent DESs and drug-eluting balloon. Despite these limitations, the study provides important insight into 2-year outcomes in patients with complex coronary lesions undergoing PCI with ZES implantation, but further longitudinal outcome studies are warranted to determine the potential benefit of the use of the newer-generation DES in complex PCI.

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REFERENCES

1. Takahashi K, Serruys PW, Fuster V, et al. Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation. *Lancet*. 2020;396:1399–1412.

2. Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of dual antiplatelet therapy: a systematic review for the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1116–1139.

3. Piccolo R, Bonaa KH, Efthimiou O, et al. Drug-eluting or bare-metal stents for percutaneous coronary intervention: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet*. 2019;6736:1–8.

4. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med*. 2020;382:1395–1407.

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5. Torii S, Jinnouchi H, Sakamoto A, et al. Drug-eluting coronary stents: insights from preclinical and pathology studies. *Nat Rev Cardiol*. 2020;17:37–51.

6. Kirtane AJ, Doshi D, Leon MB, et al. Treatment of higher-risk patients with an indication for revascularization. *Circulation*. 2016;134:422–431.

7. Endo H, Dohi T, Miyauchi K, et al. Clinical impact of complex percutaneous coronary intervention in patients with coronary artery disease. *Cardiovasc Interv Ther*. 2020;35:234–241.

8. Park J-H, Lee CH, Cho Y-K, et al. Clinical impact of lesion complexity on 2-year outcomes after zotarolimus-eluting stents implantation. *JACC: Asia*. 2021;1:332–341.

9. Banerjee S. The Resolute™ Integrity zotarolimus-eluting stent in coronary artery disease: a review. *Cardiol Ther*. 2013;2:17–25.

10. Raber L, Mintz GS, Koskinas KC, et al. Clinical use of intracoronary imaging. Part 1: Guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. 2018;39:3281–3300.

11. Soeda T, Uemura S, Park S-J, et al. Incidence and clinical significance of poststent optical coherence tomography findings one-year follow-up study from a multicenter registry. *Circulation*. 2015;132:1020–1029.

12. Otsuka K, Villiger M, Karanasos A, et al. Intravascular polarimetry in patients with coronary artery disease. *J Am Coll Cardiol Img*. 2020;13(3):790–801.

13. Otsuka K, Villiger M, van Zandvoort LJC, et al. Polarimetric signatures of vascular tissue response to drug-eluting stent implantation in patients. *J Am Coll Cardiol Img*. 2020;13:2695–2696.

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