JACC: ASIA VOL. 2, NO. 5, 2022

EDITORIAL COMMENT

Predictors of Long-Term Outcomes After Bifurcation PCI

It Still Matters*

Yohei Numasawa, MD, PhD,[a] Kentaro Hayashida, MD, PhD[b]

Percutaneous coronary intervention (PCI) for bifurcation lesions remains one of the most important and difficult challenges for interventional cardiologists even in the era of new-generation drug-eluting stents (DES) because of various lesion characteristics.[1,2] Particularly, PCI for true bifurcation lesions is associated with worse short- and long-term outcomes than for non-true bifurcation lesions.[3-6] Clinical data from the Korean bifurcation-dedicated PCI registry revealed that true bifurcation lesion was an independent predictor for side branch compromise after main vessel stenting (HR: 2.414; 95% CI: 1.268-4.597; $P = 0.007$),[4] and patients with true bifurcation lesions had a higher risk of major adverse cardiac events (MACE) than those with non-true bifurcation lesions (HR: 4.15; 95% CI: 1.01-17.1; $P = 0.05$) during a median follow-up of 36 months.[5] More recently, an Israeli single-center study reported that true bifurcation lesion was an independent predictor for 3-year MACE (OR: 3.75; 95% CI: 1.52-6.77; $P = 0.001$) among patients who underwent bifurcation PCI with second-generation DES.[6] To date, numerous studies have been conducted to investigate predictors of in-hospital or short-term outcomes, such as side branch occlusion during bifurcation PCI, especially in lesion-specific aspects.[7] However, limited data are available regarding independent predictors for long-term outcomes, particularly clinical factors, in patients undergoing bifurcation PCI.[8,9] An Italian multicenter study reported that the ACEF score, which is composed of age, creatinine, and the ejection fraction of the left ventricle, was significantly associated with long-term mortality and MACE in patients who underwent PCI for coronary bifurcation lesions.[8] However, studies investigating the different impacts of clinical and lesion-specific factors on long-term outcomes after bifurcation PCI are still lacking.

In this issue of *JACC*: Asia, Kang et al[10] reported the clinical and lesion-specific predictors of adverse outcomes after PCI for bifurcation lesions with second-generation DES, using data from the BIFURCAT (comBined Insights From the Unified RAIN and COBIS bifurcAtion regisTries) registry conducted in Korea and Italy. This study identified 5 clinical factors (age, chronic kidney disease, diabetes mellitus, current smoking, and left ventricular dysfunction) and 4 lesion-specific factors (left main disease, proximal main branch disease, side branch disease, and a small main branch diameter) that were significantly associated with the 2-year incidence of MACE. Additionally, clinical factors had a greater impact on hard endpoints, such as all-cause death and myocardial infarction, whereas lesion-specific factors were predominantly associated with lesion-oriented clinical outcomes, such as target lesion revascularization and target vessel myocardial infarction. The advantages of this study include the large sample size (N = 5,537) with a long-term follow-up from a multicenter bifurcation-dedicated registry, inclusion of a large number of patients with true bifurcation lesions (64.7%), and important statistical analyses, such as the machine learning-based LASSO (least absolute shrinkage and selection operator) regression model and area under the curve (AUC) analyses of the receiver-operating characteristic curves for verifying the discriminative performance. In this study by Kang et al,[10] the

*Editorials published in *JACC: Asia* reflect the views of the authors and do not necessarily represent the views of *JACC: Asia* or the American College of Cardiology.

From the [a]Department of Cardiology, Japanese Red Cross Ashikaga Hospital, Ashikaga, Japan; and the [b]Department of Cardiology, Keio University School of Medicine, Tokyo, Japan.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2022.07.003

JACC: ASIA, VOL. 2, NO. 5, 2022
OCTOBER 2022:619–621

incidence of MACE at 2 years after bifurcation PCI was significantly increased in patients with multiple clinical and lesion-specific predictive factors. Accordingly, the discriminative performance for MACE estimated by AUC values was improved as the number of variables, such as clinical and lesion-specific factors, increased. These findings indicated that various clinical and lesion-specific factors independently contributed to predicting adverse outcomes after bifurcation PCI. The investigators concluded that clinical and lesion-specific factors had different impacts on long-term clinical outcomes, and both should be considered for risk stratification and optimal medical care in such patients. However, the AUC value of the risk model for 2-year MACE, which included both clinical and lesion-specific variables, was modest (AUC: 0.657; 95% CI: 0.631-0.683; $P < 0.001$). Similarly, a previous multicenter study regarding bifurcation PCI reported that discrimination capacity of the ACEF score was sufficient for 30-day mortality (AUC: 0.82; 95% CI: 0.77-0.87; $P < 0.001$) and 30-day MACE (AUC: 0.73; 95% CI: 0.67-0.78; $P < 0.001$), but moderate for long-term MACE (AUC: 0.60; 95% CI: 0.57-0.62; $P < 0.001$).[8] The consistency of the modest AUC values for long-term MACE in the different studies and risk models suggests the difficulty of the precise risk prediction of long-term clinical outcomes after bifurcation PCI.

Notably, among 5 clinical factors identified in the BIFURCAT registry, age, chronic kidney disease, and left ventricular dysfunction are components of the ACEF scoring system, which is strongly associated with clinical outcomes after PCI[8] or coronary artery bypass surgery.[11] The study results by Kang et al[10] confirmed that these clinical factors are common features for predicting patients' outcomes, even in the contemporary clinical practice in bifurcation PCI. However, there may be additional essential predictors for adverse outcomes other than all 18 variables included in the BIFURCAT registry. With regard to clinical factors, the presence of anemia is strongly associated with long-term clinical outcomes, such as mortality and bleeding, in patients with coronary artery disease.[12] Furthermore, procedural factors, including the use of intracoronary imaging devices,[13,14] various stenting techniques,[2,15] and additional side branch treatment strategies such as kissing balloon inflation,[2,9,16] may contribute to the long-term clinical outcomes in patients undergoing bifurcation PCI.

Generally, details of the strategies for bifurcation PCI depend on the operators' skill, experience, judgment, and institution-specific practice. Additionally, the various methods exist for bifurcation PCI among counties worldwide because of the differences in social and medical circumstances. Indeed, a questionnaire-based study[17] showed significant differences in the basic concept of bifurcation PCI between Korea and Japan, including the frequency of the proximal optimization technique, frequency and type of 2-stent techniques, and rate of using coronary imaging devices. Additionally, the revived directional coronary atherectomy catheter is effectively used with low complication rates in combination with new-generation DES or drug-coated balloons in Japan, especially for left main bifurcation lesions.[18] These differences among various countries may contribute to the long-term clinical outcomes after bifurcation PCI, although the BIFURCAT registry-based study was conducted in 21 Korean and 15 Italian hospitals. Therefore, the lack of precise information regarding bifurcation PCI in the BIFURCAT registry and considerable procedural differences in the strategy and technique among countries may partly limit the generalizability of the study results. However, precise risk stratification is crucial, especially in patients undergoing complex PCI for true bifurcation lesions. Therefore, the study by Kang et al[10] provides important clinical implications for managing patients undergoing bifurcation PCI. Based on this study, different impacts of clinical and lesion-specific factors on long-term clinical outcomes in patients undergoing bifurcation PCI should be recognized. There is room for discussion in future perspectives, and there are still unmet needs regarding bifurcation PCI, despite advancements in device and drug technology. Hopefully, further clinical research will yield additional knowledge in this field, such as different impacts of procedure-related predictors for long-term clinical outcomes.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Kentaro Hayashida, Department of Cardiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. E-mail: khayashidamd@gmail.com.

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KEY WORDS bifurcation, clinical feature, feature selection, lesion feature, percutaneous coronary intervention