Relation of Fractional Flow Reserve After Drug-Eluting Stent Implantation to One-Year Outcomes

Chang-Wook Nam, MD, PhD\textsuperscript{a}, Seung-Ho Hur, MD, PhD\textsuperscript{a,\ast}, Yun-Kyeong Cho, MD, PhD\textsuperscript{a}, Hyoung-Seob Park, MD\textsuperscript{a}, Hyuck-Jun Yoon, MD\textsuperscript{a}, Hyungseop Kim, MD, PhD\textsuperscript{a}, In-Sung Chung, MD, PhD\textsuperscript{a}, Yoon-Nyun Kim, MD, PhD\textsuperscript{a}, Kwon-Bae Kim, MD, PhD\textsuperscript{a}, Joon-Hyung Doh, MD\textsuperscript{b}, Bon-Kwon Koo, MD, PhD\textsuperscript{c}, Seung-Jea Tahk, MD, PhD\textsuperscript{d}, and William F. Fearon, MD\textsuperscript{e}

Patients still present with drug-eluting stent (DES) failure despite an angiographically successful implantation. The aim of the present study was to investigate the relation between the fractional flow reserve (FFR) measured after DES implantation and the clinical outcomes at 1 year. A total of 80 patients (mean age 62 years, 74\% men, 99 DESs) underwent coronary pressure measurement at maximum hyperemia after successful DES implantation. The composite of major adverse cardiac events (MACE), including death, myocardial infarction, and ischemia-driven target vessel revascularization was evaluated at 1 year. The patients were divided into 2 groups (low-FFR group, FFR <0.90 and high-FFR group, FFR ≥0.90) according to the median FFR. The mean poststent percent diameter stenosis was 11 ± 5\% in the low-FFR group and 12 ± 3\% in the high-FFR group (p = 0.31). Left anterior descending coronary artery lesions were more frequent in the low-FFR group than in the high-FFR group (82\% vs 55\%, p = 0.02). The mean stent length was greater in the low-FFR group than in the high-FFR group (38 ± 18 vs 28 ± 13 mm, p = 0.01). Six cases (7.5\%) of MACE occurred during the 1-year follow-up. The rate of MACE was 12.5\% in the low-FFR group and 2.5\% in the high-FFR group (p <0.01). Receiver operating characteristic curves revealed 0.90 as the best cutoff of FFR after DES implantation for the prediction of 1-year MACE. In conclusion, a poststent FFR of ≤0.90 correlated with a greater adverse event rate at 1 year. © 2011 Published by Elsevier Inc. (Am J Cardiol 2011;107:1763–1767)

The limitations in the diagnostic accuracy of coronary angiography\textsuperscript{1} and in the clinical efficacy of drug-eluting stents (DESs)\textsuperscript{2} underscore the relevance of adjunctive techniques to more accurately evaluate the success of percutaneous coronary intervention (PCI) with DESs. Several studies have demonstrated that coronary pressure measurement has a good correlation with intravascular ultrasound findings in the evaluation of the success of PCI, thereby informing optimal stent deployment.\textsuperscript{3–7} The fractional flow reserve (FFR) can identify a residual hyperemic pressure gradient that results in abnormal resistance across both the stented and the adjacent segments. Although the FFR measured after bare metal stent implantation correlated with the 6-month clinical outcomes in a previous study,\textsuperscript{8} it is unknown whether the same applies to DES implantation. The aim of the present study was to investigate the relation between optimal physiologic DES implantation assessed by the poststent FFR and the outcomes at 1 year.

Methods

The study population consisted of 80 patients who underwent FFR measurement immediately after angiographically successful PCI with DES implantation in de novo coronary lesions. The angiographic success of PCI was defined as residual stenosis <20\% by visual assessment with Thrombolysis In Myocardial Infarction grade 3 coronary flow and FFR ≥0.80. The patients were not eligible for enrollment if they had undergone intervention in the setting of primary or emergent PCI for acute coronary syndrome, had undergone previous coronary artery bypass graft surgery, or had multiple significant lesions in the same epicardial artery, left main disease, primary myocardial disease, contraindications to adenosine, aspirin, or clopidogrel, or a major life-threatening illness. Implanted stents were commercially available DESs in all cases.

PCI was performed using standard interventional techniques. Antiplatelet and antithrombotic agents were prescribed according to the current PCI guidelines.\textsuperscript{9} All coronary angiograms were analyzed using standard definitions and measurements, which were determined according to the American Heart Association classification,\textsuperscript{10} using the guid-
The primary outcome was defined as a composite of major adverse cardiac events (MACE), defined as death, myocardial infarction, and target vessel revascularization at 12 months after the index procedure. Death was defined as all-cause mortality. Myocardial infarction was defined as threefold or greater elevation of creatine kinase-MB level or new Q waves in ≥2 contiguous leads on the electrocardiogram. Target vessel revascularization included target vessel PCI and bypass surgery of the target vessel performed in the presence of symptoms and/or signs of ischemia. Stent thrombosis was defined according to the Academic Research Consortium guidelines. In-stent restenosis was defined as ≥50% diameter stenosis on the follow-up angiogram.

Data are expressed as the mean ± SD for continuous variables and percentages for discrete variables. Continuous variables were compared using Student’s t test or analysis of variance. Categorical variables were compared using chi-square tests, nonparametric chi-square tests, or Fisher exact tests, as appropriate. Multivariate logistic regression analysis was used to assess the independent predictors of MACE. The parameters analyzed in multivariate regression analysis were selected when p < 0.10 on univariate analysis. Receiver operating characteristic curve analysis was used to determine the cutoff FFR after DES implantation for the prediction of 1-year MACE. All calculated p values were 2-sided, and differences were considered statistically significant at p < 0.05. All statistical analyses were performed using the Statistical Package for Social Sciences, version 15.0, for Windows (SPSS, Chicago, Illinois).

Results

The baseline clinical characteristics, angiographic characteristics, and quantitative coronary angiographic results are summarized in Tables 1 and 2. The average number of DESs deployed per target lesion was 1.2 ± 0.4. Three types of DESs were implanted (sirolimus-eluting stent, 51%; paclitaxel-eluting stent, 39%; and zotarolimus-eluting stent, 10%). No complications attributable to FFR measurement occurred in any of the studied patients. The patients were divided into 2 groups according to the median FFR: the low-FFR (≤0.90) group and the high-FFR (>0.90) group, with 40 patients in each group. The DES type and mean poststent percent diameter stenosis were similar between the 2 groups. The left anterior descending coronary artery (LAD) was more often stented in the low-FFR group (82%) than in the high-FFR group (55%, p = 0.02). The mean lesion length was greater in the low-FFR group (34 ± 17 mm) than in the high-FFR group (26 ± 13 mm, p = 0.02). The implanted stent length was also significantly greater in
the low-FFR group than in the high-FFR group (38/11006 18 vs 28/11006 13 mm, respectively, p = 0.01). On multivariate linear regression analysis for predicting the value of FFR after DES implantation, only the target coronary artery (LAD vs non-LAD) affected the poststent FFR significantly (β = 0.33, 95% confidence interval 0.01 to 0.07, p = 0.003), and complex lesion type showed a trend (β = 0.19, 95% confidence interval 0.01 to 0.06, p = 0.10). On multivariate logistic regression analysis, no unique independent predictor was found for 1-year MACE. The best FFR cutoff after DES implantation for the prediction of the 1-year MACE rate was 0.90 on receiver operating characteristic curve analysis (sensitivity 67%, specificity 58%, area under the curve 0.690, 95% confidence interval 0.53 to 0.86; Figure 3).

Discussion

The results of the present study have revealed, first, that the 1-year clinical outcome after DES implantation correlated with the poststent FFR; and second, that an FFR cutoff of 0.90 might be a useful indicator in daily practice for optimal physiologic DES implantation.

Although DES use has significantly reduced the rate of restenosis after PCI, 5% to 10% of stented patients develop cularization related, with the presence of angina and/or signs of ischemia. The rate of MACE and in-stent restenosis was 12.5% and 17.5% in the FFR ≤0.90 group and 2.5% and 2.5% in the FFR >0.90 group, respectively (p <0.01; Figure 1). When the patients were divided into quartiles of FFR, a similar outcome pattern was observed (Figure 2). On multivariate logistic regression analysis, no unique independent predictor was found for 1-year MACE. The best FFR cutoff after DES implantation for the prediction of the 1-year MACE rate was 0.90 on receiver operating characteristic curve analysis (sensitivity 67%, specificity 58%, area under the curve 0.690, 95% confidence interval 0.53 to 0.86; Figure 3).

Discussion

The results of the present study have revealed, first, that the 1-year clinical outcome after DES implantation correlated with the poststent FFR; and second, that an FFR cutoff of 0.90 might be a useful indicator in daily practice for optimal physiologic DES implantation.

Although DES use has significantly reduced the rate of restenosis after PCI, 5% to 10% of stented patients develop cularization related, with the presence of angina and/or signs of ischemia. The rate of MACE and in-stent restenosis was 12.5% and 17.5% in the FFR ≤0.90 group and 2.5% and 2.5% in the FFR >0.90 group, respectively (p <0.01; Figure 1). When the patients were divided into quartiles of FFR, a similar outcome pattern was observed (Figure 2). On multivariate logistic regression analysis, no unique independent predictor was found for 1-year MACE. The best FFR cutoff after DES implantation for the prediction of the 1-year MACE rate was 0.90 on receiver operating characteristic curve analysis (sensitivity 67%, specificity 58%, area under the curve 0.690, 95% confidence interval 0.53 to 0.86; Figure 3).

Discussion

The results of the present study have revealed, first, that the 1-year clinical outcome after DES implantation correlated with the poststent FFR; and second, that an FFR cutoff of 0.90 might be a useful indicator in daily practice for optimal physiologic DES implantation.

Although DES use has significantly reduced the rate of restenosis after PCI, 5% to 10% of stented patients develop
MACE within 12 months after optimal angiographic stent implantation. This might be due to angiographically apparent incomplete stent expansion, coronary dissection, dislocation of plaque at either edge of the stent, or other factors. Intravascular ultrasonography is recognized as the standard method for evaluating the PCI results. Previous studies have shown that the FFR correlates with the intravascular ultrasound findings for assessing optimal stent deployment. The poststen FFR detects a residual pressure gradient across the stented and adjacent segments that can play an important role in restenosis. Although the validation of FFR for the purpose of the assessment of optimal bare metal stent deployment was reported, our knowledge, few reports on its use in the context of DESs have been published.

In the present study, several intuitive findings were observed according to the FFR range after stent implantation. When the patients were divided according to the median FFR value, the lower FFR group had frequent LAD involvement and diffuse disease with a greater stented length compared to the greater FFR group. Although the same angiographic percent diameter stenosis was observed after DES implantation, the LAD subtends a larger myocardial territory compared to that of other major coronary arteries, resulting in a greater peak flow down the vessel and a lower poststen FFR for a given residual stenosis. Lesion length is an important geometric variable that can affect the transstenotic pressure gradient with a positive correlation. The FFR of a longer lesion and stented segment will be lower than that of a shorter lesion with the same poststen percent diameter stenosis. On linear regression analysis, the location of the target coronary artery was the only independent predictor of the FFR after DES implantation. Although statistical significance was not obtained because of the small sample size and selection bias in the study design, a complex lesion type also showed a tendency to influence the poststen FFR. This argues in favor of more careful evaluation and additional effort to obtain the optimal physiologic DES implantation when the stented lesion is long, complex, and/or occurring within the LAD.

The 1-year clinical outcome after DES implantation correlated with the FFR range in the present study. The lower the FFR, the greater the event rate. Regardless of whether the patients were divided into 2 groups or quartiles, according to the poststen FFR range, a similar pattern between the FFR and outcomes was observed (Figures 1 and 2). However, owing to the small number of studied patients and the low event rates, independent predictors for the 1-year MACE rate could not be defined on multivariate analysis. However, the FFR cutoff after DES implantation for the prediction of 1-year MACE was 0.90 on receiver operating characteristic analysis. If 0.90 were applied to these patients, 50% of the patients still had insufficient stent deployment, despite an excellent angiographic result. Even in the setting of angiographically successful stent implantation, if an adequate FFR after the procedure has not been achieved, additional evaluation can be helpful to elucidate its mechanism in these cases. Pull-back pressure recording or intravascular ultrasound examination can verify the causes of the suboptimal result, such as diffuse disease outside the stent, which puts patients at greater risk of events, or problems within the stent itself. Additional procedures, including high-pressure ballooning, deployment of an additional stent, or more aggressive medical therapy with a high-dose statin or angiotensin-converting enzyme inhibitor can be implemented. Additional study with a larger population is warranted.

The present study had several limitations. First, it was retrospective. Thus, our results were subject to selection bias. Second, the coronary pressure was measured after intracoronary injection of adenosine. Maximizing hyperemia is especially important when measuring the FFR after stenting because the detection of very small gradients is necessary to distinguish an optimally deployed stent from a suboptimally deployed stent. Because of the short hyperemic duration related to intracoronary injection, pull-back pressure measurement could not be performed in the patients with a low FFR, which might have distinguished mechanisms for a suboptimal result. Third, the number of patients included in the study was small and the duration of follow-up was short, considering the low event rate at 1-year of follow-up. No hard end points were included, limiting the power of the poststen FFR. Therefore, these results should be confirmed by larger scale studies with a longer follow-up period.

Acknowledgment: The authors thank Dr. Roberto Patarca for editorial help.


