ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2009.01.008

Baseline Fractional Flow Reserve and Stent Diameter Predict Optimal Post-Stent Fractional Flow Reserve and Major Adverse Cardiac Events After Bare-Metal Stent Deployment

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Objectives We sought to identify baseline clinical, angiographic, and hemodynamic variables associated with optimal bare-metal stent (BMS) deployment, allowing selection of patients for treatment with BMS.

Background Patients with fractional flow reserve (FFR) >0.90 after BMS have low (<6%) major adverse cardiac event rates (MACE). We hypothesized that baseline variables can predict post-stent FFR >0.90 and MACE after BMS.

Methods In 586 patients from the multicenter post-BMS FFR registry, we developed multivariable logistic regression models to identify clinical, angiographic, and hemodynamic variables associated with post-stent FFR ≥0.90 and 6-month MACE.

Results After adjusting for potential confounders, baseline FFR (odds ratio [OR]: 5.0) and stent diameter (OR: 2.5 per millimeter) were predictive of post-stent FFR >0.90. Lower FFR (OR: 7.8); smaller stent diameter (OR: 3.7 per millimeter); longer stent length (OR: 1.0 per millimeter); and larger minimal luminal diameter (OR: 2.2 per millimeter) were predictors of MACE. In patients receiving 3-mm diameter stents, baseline FFR >0.70 yielded significantly higher likelihood of achieving post-stent FFR >0.90 than baseline FFR ≤0.70 (77% vs. 63%, $p < 0.05$); and in patients receiving <3-mm diameter stents, baseline FFR <0.50 was associated with higher MACE than FFR 0.50 to 0.70, and FFR >0.70 (40% vs. 15% vs. 13%, $p < 0.05$).

Conclusions In patients receiving BMS, baseline FFR and stent diameter are predictors of post-stent FFR >0.90; and baseline FFR, stent diameter, stent length, and minimal luminal diameter are predictors of MACE. These variables may allow selection of patients who will have excellent results with BMS. (J Am Coll Cardiol Intv 2009;2:357–63) © 2009 by the American College of Cardiology Foundation

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Manuscript received April 23, 2008; revised manuscript received December 15, 2008, accepted January 9, 2009.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 2, NO. 4, 2009
APRIL 2009:357–63

Drug-eluting stents (DES) have resulted in a significant reduction in restenosis. However, there are continued concerns about late stent thrombosis (1–8), need for prolonged dual antiplatelet therapy, and higher DES cost compared with bare-metal stents (BMS).

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Fractional flow reserve (FFR) is defined as the maximal flow through a vessel in the presence of a stenosis divided by the maximal achievable flow through the vessel in the theoretic absence of the stenosis (9,10). Although FFR is most often clinically used to determine the significance of moderate coronary lesions (11), it can also be used to optimize percutaneous coronary intervention (PCI) (12–15). We have previously shown that low major adverse cardiac events (MACE) rates (<6%) can be obtained after PCI with BMS in patients who achieve post-stent FFR of >0.90 (16).

Abbreviations and Acronyms

ATP = adenosine triphosphate
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
FFR = fractional flow reserve
MACE = major adverse cardiac event(s)
MLD = minimal luminal diameter
PCI = percutaneous coronary intervention

Because post-stent FFR >0.90 is a useful surrogate for favorable long-term clinical outcome after BMS deployment, a model predicting post-stent FFR >0.90 using variables available to the operator prior to stent selection could identify patients with high probability of optimal stent deployment using BMS. Thus, we hypothesized that a model comprising baseline clinical, angiographic, and hemodynamic variables can predict a post-stent FFR >0.90 and MACE.

Methods

Study population. The current analysis is derived from the post-stent FFR registry, a multicenter registry of 750 patients from 15 hospitals (5 centers in the U.S., 5 in Europe, and 5 in Asia) who underwent PCI with BMS between January 2000 and April 2001, in which the pressure wire was used (16). The reason for use of the pressure wire was either for assessment of moderate lesions or to guide PCI. Thus, the present study population consisted of 586 of 750 patients with complete clinical, baseline FFR, post-stent FFR, and angiographic data; 164 patients were excluded from the study for the following incomplete variables: baseline FFR (n = 105), minimum lumen diameter (MLD) (n = 25), diabetic status (n = 12), artery investigated (n = 31), and stent diameter (n = 7).

Interventional procedure and measurement of FFR. Following angiography, FFR was determined using a 0.014-inch sensor-tipped high-fidelity Pressure Wire (RADI Medical, Uppsala, Sweden) in all patients as previously described (17). The pressure transducer was placed distal to the stenosis in question. Simultaneous distal coronary and aortic pressures were recorded at baseline and during maximal hyperemia. Hyperemia was induced by 1 of the following regimens: intracoronary adenosine or adenosine triphosphate (ATP), ≥30 μg in the right coronary artery and ≥40 μg in the left coronary artery; intravenous adenosine or ATP at 140 μg/kg/min; or intracoronary papaverine (15 mg for the right coronary artery and 20 mg for the left coronary artery), as previously described (16). The hyperemic capacity of these various drugs used has been shown to be equivalent (18,19). Fractional flow reserve was calculated as the ratio of the mean distal intracoronary pressure to mean aortic pressure at the time of peak hyperemia. Percutaneous coronary intervention was performed with BMS according to operator preference. The FFR measurements were made distal to the stenosis. All patients underwent successful PCI (<10% residual angiographic diameter stenosis by visual analysis), followed by post-stent FFR measurement. Quantitative coronary angiography was performed offline in all patients. Optimal post-stent FFR, defined as an FFR ≥0.90 based on favorable outcome data from the stent registry (16), and MACE represented the 2 end points of this study. We defined MACE as 6-month death, myocardial infarction, or target vessel revascularization. Procedural antithrombotic, antiplatelet, and other therapy was according the local routine of participating centers.

Statistical analysis. Clinical characteristics and angiographic and hemodynamic data were compared by univariate analysis between patients who achieved optimal post-stent FFR ≥0.90 and those with post-stent FFR <0.90. Continuous variables were compared using a *t*-test, and categorical variables were compared with the chi-square tests. Multivariable analyses were performed using logistic regression models with optimal post-stent FFR ≥0.90 and MACE as the dependent variables. When MACE was used as the dependant variable, post-stent FFR data were excluded from the multivariable analysis as this variable would not be available to the operator at the time of stent selection. All available variables were considered for the initial model, including patient demographics and medical history (age, hypertension, diabetes, hypercholesterolemia, smoking, family history of heart disease), and angiographic and hemodynamic variables (vessel location, reference diameter, diameter stenosis, MLD, stent diameter, stent length, and baseline FFR). Variables with $p < 0.05$ on univariate analysis were included in the multivariate analysis, except reference diameter, which was excluded because it reflected stent diameter (included in the model). Diabetes and hypercholesterolemia were added to the multivariable model as they were important clinical variables that might impact outcome. Odds ratios (OR), 95% confidence intervals (CI),

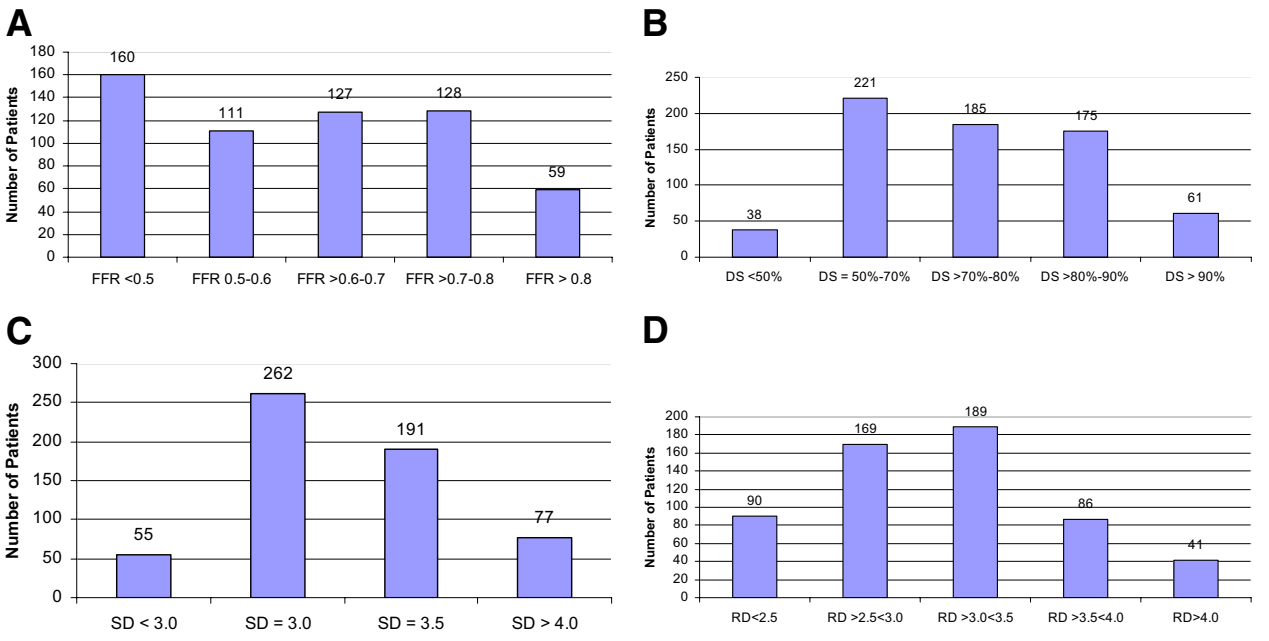

Figure 1. Distribution of Baseline Angiographic and Hemodynamic Variables

Distributions of baseline fractional flow reserve (FFR) **(A)**, diameter stenosis (DS) **(B)**, stent diameter in millimeters (SD) **(C)**, and reference diameter in millimeters (RD) **(D)**.

and p values for a post-stent FFR ≥90 and MACE were calculated from these models. Receiver-operator characteristic analysis was performed. All analyses were performed using SAS software version 9.1 (SAS Institute Inc., Cary, North Carolina). A p value of <0.05 was considered significant, and all tests were 2-tailed.

Results

The distribution of diameter stenosis, baseline FFR, stent diameter, and reference diameter in study patients is shown in Figure 1. The mean post-stent diameter stenosis was 8.1 ± 10.4% and the mean post-stent FFR was 0.92 ± 0.07. Hyperemia was induced for FFR measurement using intracoronary adenosine or ATP in 57%, intravenous adenosine or ATP in 31%, and intracoronary papaverine in 12% of patients. Of 586 patients, 424 (72%) achieved a post-stent FFR >0.90.

There were no significant differences in age or clinical risk factors, MLD, diameter stenosis, stent length, or maximal inflation pressure used for PCI between patients with post-stent FFR ≥0.90 and those with post-stent FFR <0.90 (Table 1). There were greater numbers of left circumflex arteries (17% vs. 9%, p < 0.02) and fewer left anterior descending arteries (49% vs. 64%, p < 0.01) in patients with post-stent FFR >0.90 than in those with post-stent FFR <0.90. Furthermore, significantly larger

Table 1. Baseline Patient Characteristics in Patients With Post-Stent FFR ≥0.90 or <0.90

	Post-Stent FFR ≥0.90 (n = 424)	Post-Stent FFR <0.90 (n = 162)	p Value
Mean age, yrs	62 ± 10	61 ± 11	NS
Smoking, %	48	48	NS
Hypertension, %	52	54	NS
Diabetes, %	24	27	NS
Hypercholesterolemia, %	62	62	NS
Family history of CAD, %	36	34	NS
LAD, %	49	64	<0.01
RCA, %	33	43	NS
LCx, %	17	9	0.02
Reference diameter, mm	3.08 ± 0.63	2.92 ± 0.53	<0.01
Diameter stenosis, %	73 ± 15	73 ± 17	NS
Minimal luminal diameter, mm	0.81 ± 0.49	0.76 ± 0.50	NS
Stent diameter, mm	3.3 ± 0.5	3.15 ± 0.6	<0.01
Stent length, mm	17.5 ± 7.5	18.4 ± 9.5	NS
Baseline FFR	0.62 ± 0.17	0.58 ± 0.15	<0.01
Post-stent FFR	0.95 ± 0.05	0.84 ± 0.07	—
Maximum inflation pressure, mm Hg	12.3 ± 2.6	12.4 ± 2.8	NS

CAD = coronary artery disease; FFR = fractional flow reserve; LAD = left anterior descending; LCx = left circumflex artery; NS = not significant; RCA = right coronary artery.

Table 2. MACE According to Whether a Post-Stent FFR ≤0.90 or <0.90 Was Achieved

	Post-Stent FFR >0.90 (n = 424)	Post-Stent FFR <0.90 (n = 162)	p Value
Death	3 (0.7%)	1 (0.6%)	NS
Myocardial infarction	4 (0.9%)	8 (4.9%)	<0.001
Revascularization	21 (4.9%)	24 (14.8%)	<0.001
CABG	4 (0.9%)	9 (5.5%)	<0.001
PCI	17 (4.0%)	15 (9.3%)	0.01
Any MACE	24 (5.7%)	31 (19.1%)	<0.001

CABG = coronary artery bypass graft surgery; MACE = major adverse cardiac events; PCI = percutaneous coronary angioplasty; other abbreviations as in Table 1.

Table 3. Model Predicting Post-Stent FFR >0.90

	OR	95% CI	p Value
Baseline FFR (0 to 1.0)	5.0	1.6–15.6	<0.01
Stent diameter, per mm	2.5	1.5–4.0	<0.001
Artery revascularized			
LAD vs. RCA	0.7	0.4–1.0	0.02
LCx vs. RCA	1.4	0.7–2.7	NS
Diabetes	1.1	0.7–1.7	NS
Hypercholesterolemia	1.2	0.8–1.8	NS

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

reference diameter (3.08 ± 0.63 mm vs. 2.92 ± 0.53 mm), stent diameter (3.3 ± 0.5 mm vs. 3.15 ± 0.6 mm), and higher baseline FFR (0.62 ± 0.17 vs. 0.58 ± 0.15) were observed ($p < 0.01$ for all) in patients with post-stent FFR >0.90 than in those with post-stent FFR <0.90.

As in the post-stent registry (16), we observed a significantly greater incidence of MACE in patients with post-stent FFR <0.90 versus those with post-stent FFR ≥0.90 (19.1% vs. 5.7%, $p < 0.0001$) (Table 2). This finding was driven by higher rates of myocardial infarction (4.9% vs. 0.9%, $p = 0.0023$), coronary artery bypass graft (5.5% vs. 0.9%, $p = 0.0007$), and PCI (9.3% vs. 4.0%, $p = 0.012$) in patients with post-stent FFR <0.90. There were no significant differences in death between the 2 groups (0.6 vs. 0.7%, p = NS) (Fig. 2).

In the multivariate model using post-stent FFR ≥0.90 as the dependent variable, higher baseline FFR (OR: 5.0, FFR: 0 to 1.0, 95% CI: 1.6 to 15.6) and larger stent diameter (OR: 2.5 per millimeter, 95% CI: 1.5 to 4.0) were significant predictors of post-stent FFR >0.90 (Table 3).There was a trend toward lower likelihood of achieving optimal post-stent FFR ≥0.90 in the left anterior descending artery versus the right coronary artery (0.70, 95% CI: 0.40 to 1.0). When baseline FFR was considered by decreasing increments of 0.1, the OR was 1.16 (95% CI: 1.0 to 1.3).

In the multivariate model using MACE as the dependent variable, lower baseline FFR (OR: 7.8, FFR: 0 to 1.0, 95% CI: 1.3 to 48.0), smaller stent diameter (OR: 3.7 per millimeter, 95% CI: 1.7 to 8.0), larger MLD (OR: 2.2 per millimeter, 95% CI: 1.2 to 4.0), and longer stent length (OR: 1.0 per millimeter, 95% CI: 1.0 to 1.1) were significant predictors of MACE (Table 4). When baseline FFR was considered by decreasing increments of 0.1, the OR was 1.23 (95% CI: 1.0 to 1.5). The receiver-operator characteristic analysis indicated that the C statistic for this model was 0.67.

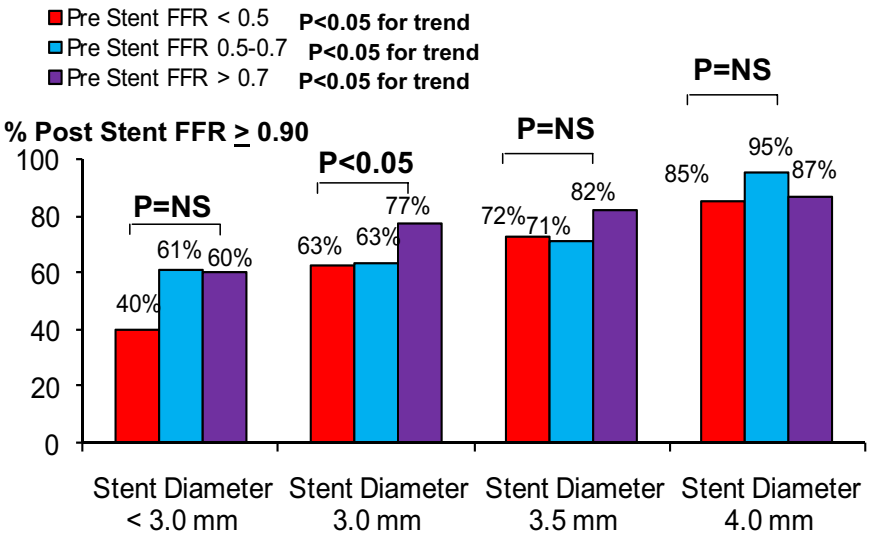

Figure 2. Proportion of Patients Achieving Post-Stent FFR ≥0.90 According to Baseline FFR and SD

Likelihood of achieving post-stent FFR ≥0.90 according to SD and baseline FFR. NS = not significant; other abbreviations as in Figure 1.

Table 4. Model Predicting MACE

	OR	95% CI	p Value
Baseline FFR (1.0 to 0)*	7.8	1.3–48.0	0.02
Stent diameter, per mm*	3.7	1.7–8.0	<0.001
MLD, per mm	2.2	1.2–4.0	0.01
Stent length, per mm	1.0	1.0–1.1	<0.01

*Decreasing values of these variables predict MACE.
MLD = minimal luminal diameter; other abbreviations as in Tables 2 and 3.

We sought to further define the relationship between stent diameter, baseline FFR, and the 2 dependant variables: post-stent FFR ≥0.90 and MACE. We found that in patients with stent diameter of 3 mm, those with baseline FFR >0.7 had significantly greater likelihood of achieving post-stent FFR ≥0.90 compared with those with baseline FFR <0.5 and 0.50 to 0.70 (77% vs. 63% vs. 63%, respectively, $p < 0.05$). The value of baseline FFR >0.70 for predicting a high likelihood of achieving post-stent FFR ≥0.90 was not observed in patients with stent diameter less than or greater than 3 mm (Fig. 2). Interestingly, in patients with stent diameter <3 mm, baseline FFR <0.50 was associated with significantly greater MACE than FFR 0.50 to 0.70, and FFR >0.70 (40% vs. 15% vs. 13%, $p < 0.05$). However, MACE was not significantly different in patients with baseline FFR 0.50 to 0.70 and >0.70 among patients with stent diameter ≥3 mm (Fig. 3).

Discussion

In the present study, using variables available to the operator prior to BMS deployment, we demonstrate that baseline FFR and stent diameter are independently predictive of post-stent FFR >0.90, and baseline FFR, stent diameter, MLD, and stent length are significant predictors of MACE. In patients receiving 3-mm diameter stents with baseline FFR >0.70, the likelihood of achieving post-stent FFR >0.90 was 77%, similar to patients receiving 3.5-mm diameter stents. In addition, among patients receiving <3-mm diameter stents, those with baseline FFR <0.50 had significantly higher MACE rates than those with FFR ≥0.50. Thus, FFR and stent dimensions may be of value in selecting lesions that can be revascularized using BMS with excellent long-term MACE rates.

There are several potential explanations for the predictive value of baseline FFR and stent diameter for optimal post-stent FFR and MACE in patients receiving BMS.

First, the lesion characteristics that reflect a higher (albeit ischemic) baseline FFR and larger stent diameter, namely, less severe stenoses, less lesional plaque burden, and larger reference vessel diameter result in larger post-stent minimal luminal areas, better stent expansion, and strut apposition (20). Post-stent FFR has been shown to correlate with post-stent intravascular ultrasound minimal luminal area, with neither correlating well with angiography (14). In support of the argument that vessels with lower atheroma burden accommodating larger BMS have good outcome, a recent study of 233 patients receiving BMS with diameters >3.5 mm had similar rates of MACE to 233 propensity matched patients treated with DES (7.7% vs. 8.5%, p = NS) (21).

Second, higher baseline FFR indicates less burden of atheroma in the whole vessel, particularly angiographically unappreciated atheroma proximal to the stented site. Thus, patients with higher baseline FFR may have less vulnerable plaques proximal to the stented site resulting in lower

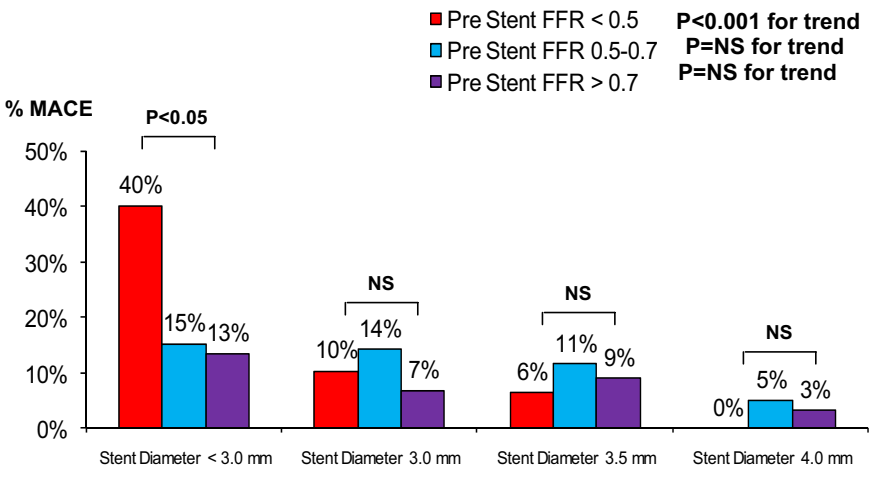

Figure 3. Incidence of MACE According to Baseline FFR and SD

Incidence of major adverse cardiac event (MACE) rates according to SD and baseline FFR. Abbreviations as in Figures 1 and 2.

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MACE rates. In support of this second explanation, compared with patients with optimal post-stent FFR, patients with suboptimal post-stent FFR not only had significantly higher rates of revascularization (14.8% vs. 4.9%, $p < 0.001$), but also higher rates of myocardial infarction (4.9% vs. 0.9%, $p < 0.001$) (16,22). We speculate that the higher rate of myocardial infarction in patients with suboptimal FFR after bare-metal stenting resulted from new plaque rupture associated with proximal diffuse atheroma rather than restenosis or stent thrombosis. To what degree the stented segment itself contributes to the final hyperemic gradient (and thus FFR) in the vessel is likely variable and depends on the stent diameter, how well the stent is deployed, and the remaining bulk of atheroma proximal to the stent. It is likely that both explanations contribute to the relationship of baseline FFR, stent diameter, and outcomes.

It is not surprising that most of the incremental prognostic value of baseline FFR with respect to MACE is seen in patients with stent diameter <3 mm. Interestingly, longer stent length and larger MLD were also significant predictors of MACE. It is well known that longer BMS lengths are associated with restenosis and thus can contribute to MACE (23). The finding that larger rather than smaller MLD was a predictor of MACE is somewhat surprising. This finding may relate to either the known inaccuracies of quantitative angiographic measures for evaluating lesion severity or the concept that it may not be lesional stenosis severity assessed by MLD, but rather the whole vessel atherosclerosis burden more accurately assessed by FFR that is the better predictor of long-term MACE.

Implications for selection of patients for BMS versus DES. There has been much recent debate and controversy regarding the association of DES with late and very late stent thrombosis (1–8,24–30). Taken together, these data suggest similar rates of death, myocardial infarction, and definite stent thrombosis between DES and BMS. However, some registries have demonstrated persistent rates of late stent thrombosis ranging from 0.2% to 0.6% per year (1,5,27). The American Heart Association, American College of Cardiology, and European Society of Cardiology have recommended careful selection of patients who receive DES largely based on whether they can tolerate and afford long-term antiplatelet therapy. Our study suggests that in addition to these considerations, baseline FFR and stent diameter can be used to help in the selection of patients who may achieve low long-term MACE rates with BMS. As it is not always clear before stent deployment which patients will have post-stent FFR ≥0.90, baseline FFR and anticipated stent diameter could assist in the decision to use a BMS or a DES. Our data indicate that patients with stent diameter of 3 mm and baseline FFR >0.70 have a significant (77%) likelihood of achieving optimal post-stent FFR with BMS. Using MACE as the outcome variable, patients receiving BMS with diameters <3.0 mm and baseline FFR <0.50 have high (40%) MACE rates and therefore should be considered for DES or bypass surgery, but that those with stent diameter <3.0 mm and FFR >0.50 may have acceptable outcomes (MACE 14%) if treated with BMS. Patients with stent diameter >3.0 mm have MACE rates <10% when treated with BMS regardless of baseline FFR, potentially obviating the need for DES. Prospective randomized studies are required to precisely answer these questions.

Study limitations. First, as a registry, this study is limited by the lack of a control arm or randomization. Additionally, the registry sample size does not allow investigation of differences between individual centers contributing data, and the modest number of MACE events limits the number of predictors that can be employed in the multivariate model without overfitting. However, this dataset is largest of its kind in patients undergoing BMS deployment with clinical, angiographic, FFR, and outcome data. Second, 164 patients from our initial multicenter registry were excluded from the present analysis due to incomplete data. However, we found no differences between patients with complete and incomplete baseline data with regard to baseline diameter stenosis (72.9% vs. 76.2%, p = NS), baseline FFR (0.60 vs. 0.64, p = NS), post-stent FFR (0.92 vs. 0.93, p = NS), and proportion of patients with post-stent FFR >0.90 (72% vs. 74%, p=NS).Third, potential patient selection bias may be introduced by the fact that all patients in this registry had pressure wire evaluation, and the pressure wire is usually used to evaluate intermediate lesions with less plaque burden. However, the average lesion diameter stenosis was 73 ± 16%, which is similar to average diameter stenosis of vessels in "real life" registries of consecutive patients undergoing PCI (31,32). Furthermore, it is known that some of the contributors to this registry used the pressure wire to assess adequate stent deployment and not intermediate lesions. Finally, pressure pullback recordings with intravenous adenosine were not systematically performed.

Conclusions

In patients undergoing BMS, baseline FFR and stent diameter predict post-stent FFR >0.90, and baseline FFR, stent diameter, stent length, and MLD are predictors of MACE. Specifically, patients receiving 3-mm diameter stents with baseline FFR >0.70 have a high likelihood of achieving post-stent FFR >0.90 and patients receiving <3-mm diameter stents with baseline FFR <0.50 have very high MACE rates at 6 months. These variables may allow selection of patients who will have excellent long-term results with BMS.

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Key Words: fractional flow reserve ■ bare-metal stents ■ percutaneous coronary interventions ■ moderate coronary lesion assessment.