# Fractional Flow Reserve Guided Percutaneous Coronary Intervention Improves Clinical Outcome with Reduced Cost in Contemporary Clinical Practice

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## Abstract

**Background:** Fractional flow reserve (FFR) is currently considered as the gold standard for evaluating the functional significance of coronary stenosis. However, its potential benefits in real-world practice remain unknown in China. This study aimed to test the hypothesis that the use of FFR is associated with improved outcome and reduced cost in Chinese real-world clinical practice.
**Methods:** A retrospective cohort study was carried out using the database of Second Affiliated Hospital of Zhejiang University, a tertiary and high-volume center in China. Clinical events were compared using the Cox proportional hazards model during a median follow-up of 13 months.
**Results:** The study cohort consisted of 366 consecutive patients referred for coronary revascularization with adjunct FFR and 366 matched controls, from 2010 to 2014. Major adverse cardiac events (MACEs) (death, myocardial infarction, repeated revascularization, or hospitalization for angina) at 4 years were found in 12.0% of angiography-guided patients and 4.9% in the FFR-guided group ($P < 0.001$). The mean number of implanted stents was significantly lower in FFR treated subjects ($0.52 \pm 0.82$ stents) compared with the angiography-guided group ($0.93 \pm 0.96$ stents) ($P < 0.001$). No difference in overall costs at initial hospitalization was observed between angiography-guided percutaneous coronary intervention (PCI) compared with FFR-guided PCI (RMB 33,000 Yuan, range: RMB 7393–44,700 Yuan) versus RMB 21,200 Yuan (RMB 19,100–47,100 Yuan) ($P = 0.54$). However, costs for MACEs during follow-up were significantly reduced in the FFR-guided arm ($P < 0.001$).
**Conclusions:** In the contemporary clinical practice, FFR-guided PCI is associated with decreased use of stents, improved clinical outcome, and reduced costs, compared with angiography-guided PCI.

**Key words:** Costs and Cost Analysis; Fractional Flow Reserve; Myocardial Percutaneous Coronary Intervention; Prognosis

## Introduction

Over the past few decades, percutaneous coronary intervention (PCI) has become one of the most common medical procedures for patients with coronary artery disease. The benefits of PCI are mainly attributable to a reduction of myocardial ischemia.[1] However, noninvasive tests of myocardial ischemia are limited by their poor sensitivity in localizing the lesions.[2] Fractional flow reserve (FFR) is a pressure-wire based index used during the invasive procedure to identify myocardial ischemia.[3] FFR is now considered as the gold standard for evaluating the functional significance of coronary stenosis.[3,4] Despite increasing evidence demonstrating the utility of FFR in different patient subsets, its use is still limited in clinical practice.[5,6] Indeed, the operator's decision whether or not to use FFR in real-world practice is often based on angiographic findings, which often provide inaccurate data for stenosis.[7] FFR's potential benefits in real-world practice remain unknown in China. Meanwhile, revascularization in patients with coronary artery disease is among the most common major medical procedures in China. Approximately, 2.5 million Chinese suffer from myocardial infarction, generating hospitalization costs of RMB 4.9 billion Yuan as assessed in 2012.[8] In addition, total 454, 505 PCI were performed in 2013 in China. Unfortunately, studies assessing the benefits of FFR in Chinese real-world practice are scarce. In addition, the use of FFR is still limited in China due to the lack of financial support. Hence, this study aimed to test the hypothesis that the use of FFR is associated with improved outcome and reduced cost in Chinese real-world clinical practice.

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## Methods

### Subjects

This was a retrospective study using the database of Second Affiliated Hospital of Zhejiang University, a tertiary and high-volume center in China. FFR measurement was first introduced in this center in 2010, and patients were recorded in a registry starting July 2010. Therefore, consecutive patients referred for coronary revascularization with adjunct FFR between July 2010 and July 2014 were included in this study. A matched cohort design was used, with the control group matched for gender, age (in 5-year age bands), date of admission (in 3-month bands) and Gensini score,[9] at a ratio of 1:1. Exclusion criteria comprised myocardial infarction within 5 days of PCI; previous coronary bypass surgery (coronary artery bypass grafting); cardiogenic shock, rheumatic heart disease, and congenital cardiovascular diseases; serious concomitant disease, reduced life expectancy (<2 years); pregnancy in women. This study was approved by the institutional review board and carried out according to the principles of the *Declaration of Helsinki*.

### Coronary angiography and fractional flow reserve assessment

Invasive coronary angiography was performed using 4–7 F guiding catheters through the radial or femoral approaches. Patients receiving a stent were pretreated with clopidogrel (300–600 mg) and aspirin (100–300 mg). Then, patients were prescribed statins, lifelong aspirin use, and clopidogrel for 3–6 months (after implantation of bare metal stents) to 12 months (after implantation of drug-eluting stents) after PCI. The severity of luminal narrowing was assessed visually. The intracoronary pressure of intermediate lesions was measured with a coronary pressure wire (St. Jude Medical, Minneapolis, MN, USA). PCI was performed in patients with FFR <0.75, and deferred in those with FFR >0.80. For patients with FFR values between 0.75 and 0.80, the decision regarding revascularization was left to the operator's discretion.

### Outcome measures

Patients were clinically followed up at 1, 6, and 12 months, and annually thereafter, via office visits or telephone contact. The primary outcome measure during follow-up was major adverse cardiac events (MACEs), defined as composite of death from any causes, myocardial infarction, any repeat revascularization, and hospitalization for angina. Secondary outcome measures were number of implanted stents and cost of the different strategies.

### Statistical analysis

The study population was analyzed according to the different diagnostic strategies (FFR and angiography) used. Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]). The cost of events during follow-up was presented as median (min, max). Categorical data were presented as number (percentage) of patients. Group comparisons were assessed using Student's two-sample *t*-test or the Mann-Whitney *U*-test for continuous variables, and Pearson's $\chi^2$ test or the Fisher's exact test for categorical data. Survival curves were constructed using a multivariate Cox proportional hazards model, after adjusting for age, gender, coronary risk factors (hypertension, hypercholesterolemia, current smoker, diabetes mellitus, body mass index, family history), and Gensini score.[9] A two-sided $P < 0.05$ was considered as statistically significant. The SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses.

## Results

### Baseline characteristics

From July 2010 to July 2014, a total of 732 patients were enrolled. Baseline characteristics in the two groups were similar: Age, gender, coronary risk factors, prior PCI, prior myocardial infarction, left ventricular ejection fraction, clinical presentation, and discharge medications except clopidogrel. Table 1 summarizes the baseline characteristics of the study population.

### Angiography and procedural characteristics

Angiography and procedural characteristics of patients are summarized in Table 2. In total, 366 patients undergoing

**Table 1: Baseline characteristics**

| Items | Angiography group (*n* = 366) | FFR group (*n* = 366) | *P* |
|---|---|---|---|
| Age, years, mean±SD | 63.4 ± 9.2 | 63.5 ± 9.4 | 0.90 |
| Male, *n* (%) | 282 (77.0) | 282 (77.0) | 0.95 |
| BMI, kg/m$^2$, mean±SD | 24.4 ± 2.9 | 24.0 ± 3.0 | 0.052 |
| Hypertension, *n* (%) | 250 (68.3) | 253 (69.1) | 0.97 |
| Hypercholesterolemia, *n* (%) | 101 (27.6) | 121 (33.1) | 0.11 |
| Current smoker, *n* (%) | 121 (33.1) | 119 (32.5) | 0.96 |
| Diabetes mellitus, *n* (%) | 93 (25.4) | 116 (31.7) | 0.06 |
| Family history, *n* (%) | 28 (7.7) | 23 (6.3) | 0.49 |
| Previous myocardial infarction, *n* (%) | 67 (18.3) | 49 (13.4) | 0.07 |
| Previous PCI, *n* (%) | 161 (44.0) | 140 (38.3) | 0.12 |
| Left ventricular ejection fraction, %, mean±SD | 63.9 ± 8.9 | 64.3 ± 8.5 | 0.46 |
| Clinical presentation, *n* (%) | | | |
| Stable angina | 161 (44.0) | 150 (41.0) | 0.41 |
| Unstable angina | 199 (54.4) | 209 (57.1) | 0.46 |
| ST-elevation myocardial infarction | 1 (0.27) | 2 (0.54) | 1.00* |
| Non-ST-elevation myocardial infarction | 5 (1.4) | 5 (1.4) | 1.00* |
| Discharge medications, *n* (%) | | | |
| Beta-blocker | 274 (74.9) | 257 (70.2) | 0.18 |
| Calcium antagonist | 117 (32.0) | 114 (31.1) | 0.83 |
| Nitrate | 168 (45.9) | 151 (41.3) | 0.22 |
| ACE inhibitor or ARB | 289 (79.0) | 272 (74.3) | 0.16 |
| Statin | 363 (99.2) | 362 (98.9) | 0.10 |
| Aspirin | 349 (95.4) | 342 (93.4) | 0.33 |
| Clopidogrel | 322 (88.0) | 294 (80.3) | 0.004 |

*Fisher's exact test. SD: Standard deviation; FFR: Fractional flow reserve; BMI: Body mass index; PCI: Percutaneous coronary intervention; ACE inhibitor: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker.

FFR were matched with 366 individuals to be treated with angiography-guided PCI. The number of indicated lesions and severity of coronary artery disease (as indicated by Gensini scores) were similar between both groups. A total of 24.9%, 36.6% and 38.5% of patients in the angiography group had three-, two- and one-vessel disease, respectively; meanwhile, values of 24.6%, 35.8% and 39.6% were obtained for the FFR group ($P > 0.05$). However, more patients had left anterior descending artery stenosis in the FFR group ($P < 0.05$). In addition, the number of patients that underwent PCI was significantly reduced in the FFR-guided arm (34.4% vs. 63.1%, $P < 0.001$); idem for the mean number of implanted stents and treated lesions, although similar numbers of lesions were obtained in both groups. Interestingly, the overall stent length needed was shorter in the FFR-guided group. Finally, significant differences in multi-vessel stenting were observed in the angiography-guided PCI group compared with patients treated with FFR-guided PCI (6.3% vs. 1.1%, $P < 0.001$).

**Table 2: Angiography and procedural characteristics of the patients**

| Characteristics | Angiography group ($n$ = 366) | FFR group ($n$ = 366) | $P$ |
|---|---|---|---|
| Extent of vascular disease, $n$ (%) | | | |
| One-vessel disease | 141 (38.5) | 145 (39.6) | 0.74 |
| Two-vessel disease | 134 (36.6) | 131 (35.8) | 0.78 |
| Three-vessel disease | 91 (24.9) | 90 (24.6) | 0.95 |
| LM | 5 (1.4) | 4 (1.1) | 1.00* |
| RCA | 187 (51.1) | 178 (48.6) | 0.51 |
| LCX | 164 (44.8) | 154 (42.1) | 0.46 |
| LAD | 270 (73.8) | 297 (81.1) | 0.01 |
| Extent of occlusion, number of lesions/total number (%) | | | |
| 50–70 narrowing | 515/899 (57.3) | 699/931 (75.1) | |
| 71–90 narrowing | 343/899 (38.2) | 211/931 (22.6) | |
| 91–99 narrowing | 31/899 (3.4) | 11/931 (1.2) | |
| Total occlusion, % | 10/899 (1.1) | 10/931 (1.1) | |
| Gensini score, mean±SD | 22.4 ± 17.1 | 20.7 ± 13.4 | 0.13 |
| Number of lesions per patient, mean±SD | 2.46 ± 1.5 | 2.54 ± 1.5 | 0.461 |
| Number of stents per patient, mean±SD | 0.93 ± 0.96 | 0.52 ± 0.82 | <0.001 |
| Number of treated lesions per patient, mean±SD | 0.81 ± 0.88 | 0.43 ± 0.67 | <0.001 |
| Total stent length per patient, mm, mean±SD | 22.92 ± 26.69 | 13.06 ± 22.23 | <0.001 |
| Multi-vessel stenting, $n$ (%) | 23 (6.3) | 4 (1.1) | <0.001* |

*Fisher's exact test. SD: Standard deviation; FFR: Fractional flow reserve; LM: Left main; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery.

## Costs

Economic evaluation for each strategy included costs of initial hospitalization as well as events during follow-up. In this study, only costs specific to either strategies were included. Costs of initial hospitalization were calculated for the actual materials used and medicine consumption. Guiding catheters, regular wires, pressure wires, balloon dilatation catheters, and stents were taken into consideration. The cost of events during follow-up was calculated for the actual consumption of MACE by determining death from any causes, myocardial infarction, any repeated revascularization, and hospitalization for angina. Costs for all items are shown in Table 3. The overall costs of initial hospitalization in the FFR group were similar with those obtained for the angiography group (RMB 33,000 Yuan, ranging from RMB 7393 to 44,700 Yuan vs. RMB 21,200 Yuan, ranging from 19,100 to 47,100, $P = 0.54$). However, significantly reduced costs for MACE during follow-up were observed in the FFR-guided arm compared with the angiography group (RMB 0 Yuan, ranging from RMB 0 to 95,181 Yuan vs. RMB 0 Yuan, ranging from RMB 0 to 102,401 Yuan, $P < 0.001$).

## Clinical outcomes

Median follow-up durations were 13 months and 13.5 months in the angiography and FFR groups, respectively, indicating no significant difference. The number of patients lost to follow-up were 21 (5.7%) in the angiography group and 16 (4.4%) in the FFR group. Of the 804 deferred lesions in the FFR group, 10 (1.24%) were revascularized during follow-up. Particularly, among 235 deferred patients in the FFR group, 3 (1.27%) had myocardial infarction (one patient died) and 5 (2.13%) repeated revascularizations. Cox multivariable model estimates of MACE (4.9% vs. 12.0%, $P < 0.001$) and hospitalization for angina (4.9% vs. 11.2%, $P = 0.001$) at 4 years showed lower values in the FFR arm compared with patients treated with angiography-guided procedure [Figure 1]; on the other hand, the rates of mortality, myocardial infarction, and repeated revascularization were comparable between the two groups [Table 4].

**Table 3: Costs of FFR and angiography strategies (RMB, Yuan)**

| Items | Angiography group ($n$ = 366) | FFR group ($n$ = 366) | $P$ |
|---|---|---|---|
| Overall costs of initial hospitalization | 33,000 (7393, 44,700) | 21,200 (19,100, 47,100) | 0.54 |
| Costs of materials* | 23,600 (1215, 34,200) | 12,800 (11,900, 35,800) | 0.53 |
| Costs of medicine | 2473 (1847, 3149) | 2469 (1815, 3272) | 0.91 |
| Cost of events† | | | |
| During follow-up | 0 (0, 102,401) | 0 (0, 95,181) | <0.001 |
| Overall costs‡ | 34,400 (7892, 49,000) | 21,300 (19,100, 47,400) | 0.74 |

*Guide catheter, guidewire, pressure wire, balloon catheter, stents and other materials used at initial procedure; †Death from any causes, myocardial infarction, any repeat revascularization, and hospitalization for angina; ‡The sum of the overall costs of initial hospitalization and the cost of events during follow-up. FFR: Fractional flow reserve.

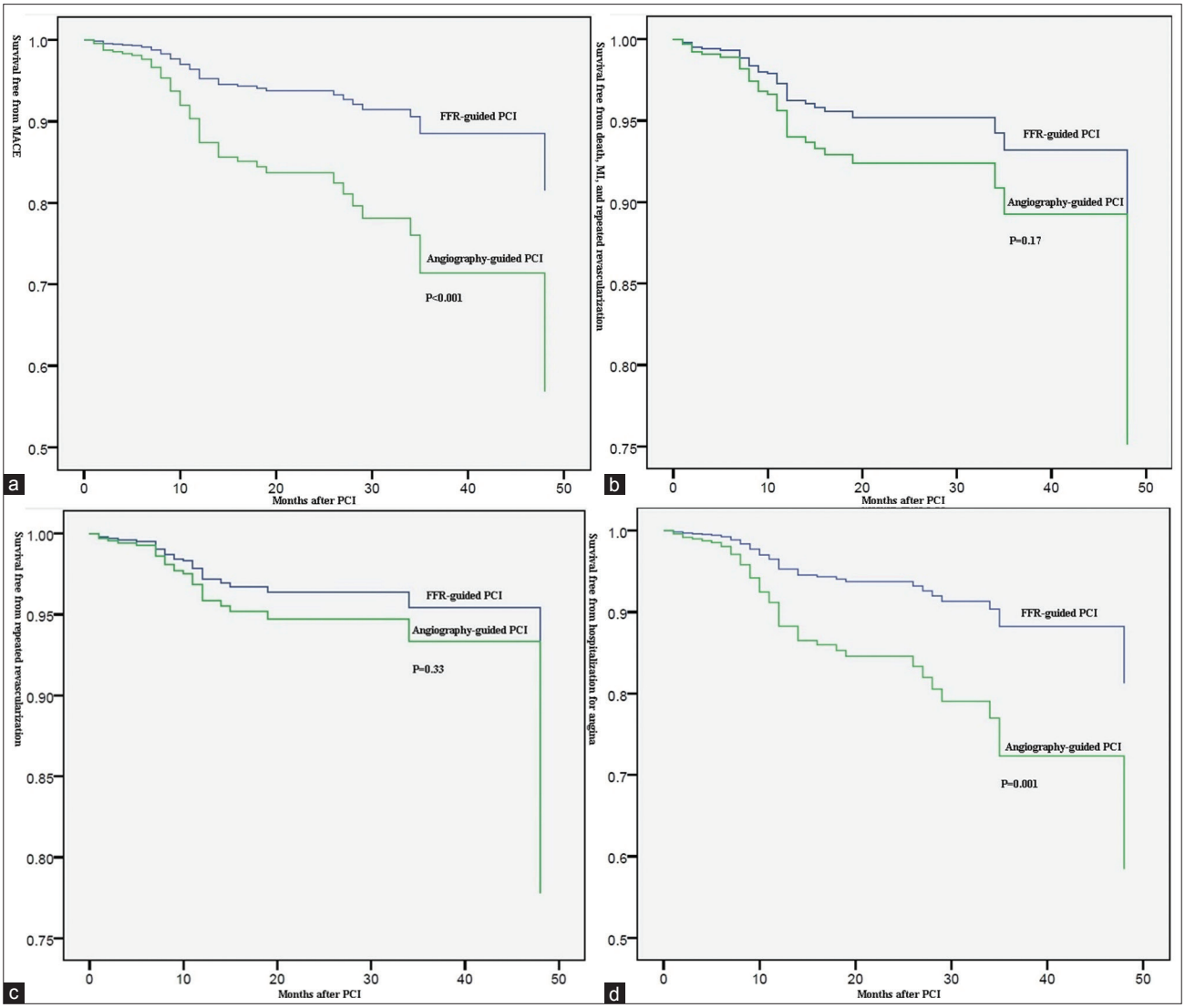


**Figure 1:** Cox regression survival curves according to study group. (a) Primary outcome of death from any causes, myocardial infarction, any repeated revascularization, and hospitalization for angina; (b) death from any causes, myocardial infarction, and any repeated revascularization; (c) any repeated revascularization; (d) hospitalization for angina.

**Table 4: Clinical outcomes between July 2010 and October 2014**

| Events | Angiography group ($n$ = 366) | FFR group ($n$ = 366) | $P$ | Adjusted *HR** with FFR guidance (95% *CI*) |
|---|---|---|---|---|
| In-hospital stay, days, mean±SD | 3.60 ± 2.00 | 3.71 ± 2.67 | 0.52 | |
| Follow-up time, m, median (IQR) | 13.0 (9.0, 21.8) | 13.5 (9.0, 22.0) | 0.76 | |
| MACE, *n* (%) | 44 (12.0) | 18 (4.9) | <0.001 | 0.36 (0.20–0.64) |
| Death, *n* (%) | 5 (1.4) | 1 (0.3) | 0.096 | 0.15 (0.02–1.40) |
| MI, *n* (%) | 4 (1.1) | 3 (0.8) | 0.72 | 0.75 (0.16–3.60) |
| Revascularization, *n* (%) | 17 (4.6) | 12 (3.3) | 0.33 | 0.68 (0.31–1.49) |
| Hospitalization for angina, *n* (%) | 41 (11.2) | 18 (4.9) | 0.001 | 0.39 (0.22–0.69) |
| Death/MI/revascularization, *n* (%) | 23 (6.3) | 15 (4.1) | 0.17 | 0.62 (0.31–1.23) |

*Adjusted for age, gender, BMI, smoking history, diabetes, hypertension, hypercholesterolemia, family history, and Gensini score. SD: Standard deviation; IQR: interquartile range; FFR: Fractional flow reserve; *HR*: Hazard ratio; *CI*: Confidential interval; MACE: Major adverse cardiac event; MI: Myocardial infarction; BMI: Body mass index.

## Discussion

FAME[10] and FAME2[11] assessing the value of FFR-guided PCI demonstrated reduced rates for MACEs. However, data regarding the effect of FFR-guided PCI in real-world practice are sparse in China. The current study, to our knowledge, examined the largest number of patients treated with FFR-guided PCI in China. This cohort study, with median follow-up of 13 months revealed the benefits of FFR-guided PCI in an actual patient population. FFR-guided PCI, compared with the strategy using angiography,

significantly reduced the rate of the primary composite outcome (MACE) during follow-up. This is primarily due to a decreased rate of hospitalization for angina. The presence and extent of inducible ischemia are the most important prognostic factor among patients with coronary artery disease.[12] FFR-guided PCI probably reduces the rate of hospitalization for angina by allowing a more judicious use of stents and equal relief of ischemia. On the other hand, the high rate of stent implantation deferral obtained after FFR measurement can help avoid the risk of thrombosis, restenosis, and unexpected device-related diseases associated with stent placement.[13-15] While the primary composite end point was improved by FFR, secondary end points, including death, myocardial infarction, and repeated revascularization, showed no significant differences, in agreement with a recent large cohort study.[16] A recent observational study from the Mayo Clinic also detected no survival benefit for FFR-guided PCI using Cox multivariable models.[17] Fröhlich *et al*.[16] suggested that FFR-guided PCI may have a stent sparing effect, which does not translate into a survival benefit. Although FFR is now considered as the gold standard for evaluating the functional significance of coronary stenosis, its use is still limited.[5,6] Park *et al*.[18] reported that routine measurement of FFR in daily practice appears to be associated with improved clinical outcomes, where FFR use during PCI increased from 1.9% to 50.7% in 4 years, suggesting that irregular measurement of FFR may weaken the survival benefit of FFR-guided PCI in real-world practice.

PCI is performed without documentation of inducible ischemia and is associated with high economic costs.[19] Subgroup analysis of the FAME study revealed that FFR-guided PCI results in significant cost-savings by reducing stent use, rehospitalization rate, and MACE.[20] Similarly, the FAME 2 sub-study showed an incremental cost-effectiveness ratio of $36,000 perquality-adjusted life-year for FFR-guided PCI.[21] In the FAME study, universal stenting of lesions with angiographic stenosis >50% cannot be justified in real-world practice, let alone economic grounds. In the current study, FFR use did not seem to decrease the overall costs of initial hospitalization. Among 366 patients in the angiography-guided group, 134 (36.6%) PCI-deferred patients were found. FFR measurement costs nearly RMB 10,000 Yuan in China. Hence, the overall costs of initial hospitalization of PCI-deferred patients are higher in the FFR-guided group, weakening the benefit of fewer stents used. In the subsequent years, mean costs for MACEs during follow-up were higher in the angiography-guided arm ($P < 0.001$). This was primarily due to higher rates of revascularization and hospitalization for angina.

A few limitations of this study should be mentioned. The sample size was determined based on FFR volume in a single-site, and a retrospective matched cohort study has limitations inherent to nonrandomized trials. In addition, coronary lesions were assessed visually, rather than by quantitative coronary angiography. Finally, we had no detailed information on costs of resources used at initial procedure; idem for secondary preventive medications during follow-up.

In conclusion, FFR-guided PCI in daily practice is associated with the implantation of fewer stents, and improved clinical outcome, which is primarily due to decreased hospitalization for angina. In addition, the FFR-guided strategy also reduced costs during follow-up.

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