Original Article

Cost-effective Analysis of the Fractional Flow Reserve in an Iranian Cohort With Multivessel Coronary Artery Disease

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ABSTRACT

Background: The fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) has proven effective in decreasing cardiac events by comparison with all-comers stenting. In this study, we aimed to evaluate the cost-effectiveness of this method in an Iranian population.

Methods: In this prospective cohort, patients with moderate stenosis (50%–70% severity) were included, while those with acute coronary syndrome were excluded. The patients were divided into 2 groups: the FFR group, for whom revascularization was performed based on FFR results, and the control group, for whom revascularization was performed based on the interventionist's assessment. An FFR of less than 0.80 was considered ischemic in this investigation.

Results: A total of 188 patients with moderate coronary artery lesions scheduled for elective PCI were included: 98 patients were assigned to the FFR group and 90 to the control group. Readmission and major adverse cardiac events (MACE) were decreased significantly in the FFR group (24.4% vs 11.2%; $P = 0.017$ and 25.6% vs 12.2%; $P = 0.019$, respectively). The quality-adjusted life-year (QALY) value was improved in the FFR group in comparison with the control group (0.8643 ± 0.0961 vs 0.7449 ± 0.10139, respectively; $P < 0.001$), resulting in a lower cost for each QALY in the FFR group than in the control group (131 395 349 QALY/rials vs 210 666 667 QALY/rials, respectively; $P < 0.001$). Additionally, our calculation of the incremental cost-effectiveness ratio showed that the cost-effectiveness of the FFR utilization was at least 409 million rials and at most 431 million rials for each QALY, depending on the inclusion of the cost of the FFR catheter.

Conclusions: Our results demonstrated the effectiveness of FFR in diminishing MACE. The method was cost-effective according to various calculation methods in an Iranian population. ***(Iranian Heart Journal 2020; 21(3): 55-63)***

KEYWORDS: Percutaneous coronary intervention, Fractional flow reserve, Cost-effectiveness

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Received: June 17, 2019 **Accepted:** July 20, 2019

Percutaneous coronary intervention (PCI) has been shown to improve patients' symptoms, quality of life, and specific clinical outcomes. [1] Nonetheless, reliance on anatomical involvement may render the superiority of revascularization over medical therapy questionable. [2] Classically, coronary angiography was the main method for evaluating the involvement of the coronary arteries, but the assessment was limited to anatomical involvement. [3,4] This limitation becomes more apparent when the operator faces moderate plaques, in which visual assessment has only 56% accuracy in detecting ischemic lesions. [5] Although noninvasive tests might be able to discern the culprit lesion, they are incapable of a precise depiction of ischemic lesions in multivessel coronary artery disease. [6]

The fractional flow reserve (FFR) is a novel method to estimate the ischemic burden of stenosis. By comparison with noninvasive methods, this index is specific and has a superior spatial resolution on the strength of its potential to analyze each arterial segment separately. [7] The routine measurement of FFR in patients with multivessel disease has been shown to lessen not only the rate of the composite endpoint of death, nonfatal myocardial infarction, and repeat revascularization [3] but also the rate of urgent revascularization compared with medical therapy alone. [8]

Despite this intriguing achievement, FFR has a considerable additive cost on routine coronary angiography and needs a special facility in the catheterization laboratory. Several studies have clearly demonstrated the cost-effectiveness of FFR as a routine practice inasmuch as it significantly reduces unnecessary stenting. [5,9], [10] Since its introduction, FFR has been utilized in Iran; still, due to a lack of locally specific cost-benefit analyses, the procedure is not reimbursed by insurance companies. Accordingly, in the present investigation, we sought to conduct a cost-effective analysis of FFR-guided PCI in a tertiary cardiovascular center in Iran. To our knowledge, there is no previous report on the cost-benefit analysis of FFR in the Iranian population.

METHODS

The present study was a prospective cohort of all patients with moderate stenosis (50%–70% severity by visual assessment) who were potential candidates for PCI, and it excluded those with acute coronary syndrome. The patients were divided into 2 groups: the FFR group, for whom revascularization was performed based on FFR results, and the control group, for whom revascularization was performed based on the visual assessment and clinical judgment of interventional cardiologist. The study protocol was approved by the Ethics Committee of Rajaie Cardiovascular Medical and Research Center, and signed informed consent was obtained from the study population.

FFR was performed in accordance with the latest recommendations, and an FFR of less than 0.80 was considered the cutoff point for an ischemic lesion.

Main Outcomes

The main outcomes of this study were as follows:

1. Major adverse cardiac events (MACE): MACE comprised death due to cardiac complications, myocardial infarction, and readmission due to cardiac events. The incidence of these outcomes was considered a composite endpoint.
2. Quality of life/health utility: This outcome was investigated by using a visual analog scale (VAS) and the European Quality of Life Questionnaire

(EQ-5D). Our study patients were asked to score their health status and quality of life, with 0 representing death and 100 representing a state of complete health and life satisfaction. The evaluation was done twice: first after angiography and then after the whole follow-up.

3. Costs: The costs were divided into primary and follow-up costs. The primary costs were comprised of primary diagnostic and therapeutic expenses during hospitalization, while the follow-up costs encompassed medication and readmission expenses. The information was obtained from the patients, the patients' hospital records, and the finance department of the hospital.
4. Cost-effectiveness: The evaluation of the indices of cost-utility analysis was also one of the major outcomes of the current study.

Follow-up: In the present study, the patients were followed for 12 months. The follow-up of the study population was conducted in 2 ways: by telephone calls every 3 months to inquire about medications, clinical complications, and any possible changes in the therapeutic process or prescribed medications and by contacting the patients in their routine visits to outpatient clinics. Hospital records were used in the case of the patients who were readmitted. At the end of the 12th month, the patients were asked to visit the clinic for a re-evaluation of their quality of life. Accordingly, the quality-adjusted life-year (QALY) was measured. There was no lost case during the follow-up.

Statistical Analysis

The mean ± the standard deviation (SD) and the frequency index (%) were used to describe the numerical and qualitative variables, respectively. Data comparison between the 2 groups was performed using the independent sample *t*-test for the numerical variables. The Mann–Whitney *U*-test was employed to rank the variables, and the Pearson χ^2 test (or the Fisher exact test) was applied for the nominal variables. Survival analysis was performed to assess the time and the probability of the occurrence of the clinical outcomes using the Kaplan–Meier curve, and the log-rank test was utilized to compare the groups. For the statistical analyses, statistical software IBM SPSS Statistics 25 for Mac (IBM Inc, Armonk, NY) was used.

RESULTS

In the present study, conducted between April 2016 and September 2017, a total of 188 patients (133 men/58 women) at an average age of 58 ± 10 years were selected and followed for 1 year. The patients were divided into 2 groups of FFR (n = 98) and control (n = 90). The baseline characteristics of the 2 groups are depicted in Table 1.

Table 1: Demographic, clinical, and angiographic characteristics in the FFR and control groups

Characteristic	Control (n=90)	FFR (n=98)	*P* value
Age (y) (mean ± SD)	58 ± 10.6	59 ± 9.90	0.416
Gender (F/M)	25/65	30/68	0.670
Diabetes (%)	30 (33.3%)	26 (26.5%)	0.308
Hypertension (%)	51 (56.7%)	55 (56.1%)	0.940
Smoking (%)	43 (47.8%)	34 (34.7%)	0.070
Dyslipidemia (%)	34 (37.8%)	42 (42.9%)	0.478
Family history (%)	15 (16.7%)	25 (25.5%)	0.139
CAD anatomical involvement			0.462
Single-vessel	75 (83.3%)	86 (87.8%)	
Double-vessel	14 (15.6%)	12 (12.2%)	
Triple-vessel	1 (1.1%)	0	
NYHA Functional Class			0.666
I	41 (47.1%)	39 (40.6%)	
II	38 (43.7%)	48 (50%)	
III	8 (9.2%)	9 (9.4%)	

CAD, Coronary artery disease; FFR, Fractional flow reserve; NYHA, New York Heart Association

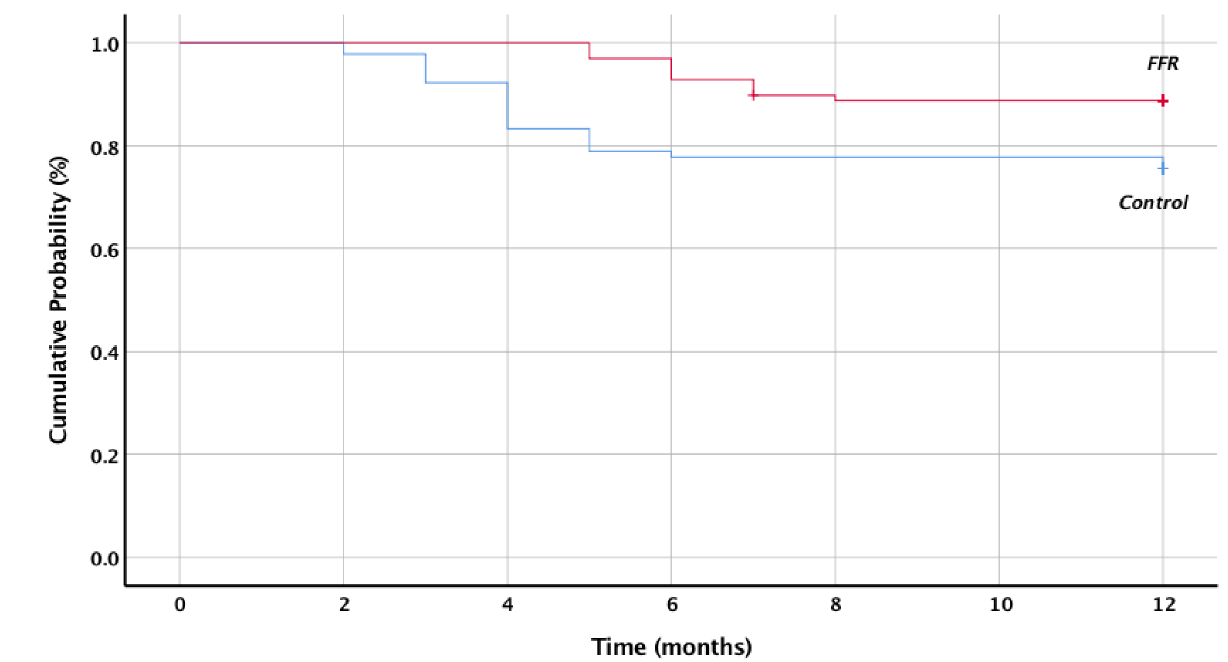
In the FFR group, 24 (24.5%) patients had an FFR of less than 0.80 and were, consequently, candidated for PCI. The other 74 (75.5%) patients in the FFR group, who had an FFR of greater than 0.80, were placed on medical therapy. In the control group, based on the traditional approach, all the patients were treated via PCI.

The incidence of hard cardiac endpoints was compared between the 2 groups over the 1-year follow-up period (Table 2). Readmission and MACE were significantly decreased in the FFR group compared with the control group. The onset time of complications was recorded in the 2 study groups. The event-free time was 11 months for the FFR group and 10 months for the control group. The event-free time was then analyzed using the Kaplan–Meier survival analysis, and the result showed that the occurrence of readmission in the FFR group was about 3 months later than that in the control group. Additionally, the possibility of the nonoccurrence of readmission in the FFR group (90%) was higher than that in the control group (78%) (Fig. 1).

Table 2: Incidence of cardiac events and readmission in the FFR and control groups

Event	Control (n=90)	FFR (n=98)	*P* value
Mortality	3 (3.3%)	1 (1%)	0.227
Readmission	22 (24.4%)	11 (11.2%)	0.017
Myocardial infarction	2 (2.2%)	0	0.228
MACE	23 (25.6%)	12 (12.2%)	0.019

FFR, Fractional flow reserve; MACE, Major adverse cardiac events



Mean of the event-free Time (95% CI) (mon)		*P* value (log-rank test)
Control	FFR	
10.2 (9.5 – 10.9)	11.3 (11 – 11.7)	0.011

FFR, Fractional flow reserve.

Figure 1: Kaplan–Meier chart for comparing the probability of readmission-free periods between the FFR and control groups

Table 3: Comparisons of primary (hospitalization) costs between the FFR and control groups

Cost	Control (n=90)		FFR (n=98)		*P* value
	mean	SD	mean	SD	
Physician fees	3,548,048	4,945,759	2,422,452	1,540,708	0.002
Costs of the cath lab	37,994,242	17,011,616	23,495,750	12,942,907	<0.001
Costs of surgical and operating rooms	7,411,413	5,197,176	5,131,662	3,337,405	<0.001
Costs of anesthesia	2,409,928	3,354,511	1,794,937	1,667,388	0.018
Costs of imaging	566,313	1,325,254	476,475	1,031,361	0.437
Costs of paraclinical care	3,628,173	2,265,832	2,639,122	1,083,788	<0.001
Costs of pharmaceutical care	57,273,675	39,743,314	33,618,179	18,152,933	<0.001
Miscellaneous costs	187,061	581,162	131,795	318,275	0.226
Bed-related costs	6,674,389	7,814,057	3,995,335	2,627,845	<0.001
Total primary costs (with FFR catheter costs)	119,797,509	70,732,933	95,601,932	34,857,775	<0.001
All costs are in rials. Cost of the FFR catheter was considered 22 million rials.					

FFR, Fractional flow reserve

Table 4: Comparisons of the costs during the first year of follow-up between the FFR and control groups

Cost	Control (n=90)		FFR (n=98)		*P* value
	mean	SD	mean	SD	
Costs of medication	6,000,000	1,003,510	1,846,226	2,737,970	<0.001
Costs of readmission	32,227,490	6,213,860	15,566,040	4,585,326	0.002
Total cost of the 1-year follow-up	38,227,490	6,213,860	17,412,266	4,959,346	<0.001
All costs are in rials.					

Cost analysis: The costs of the patients in this study were evaluated at 2 levels of primary costs and follow-up costs. The primary costs were defined as diagnostic and therapeutic costs of the patients during hospitalization such as physician fees; pharmaceutical and paraclinical expenses; and the costs of the cath lab, operating rooms, anesthesia, imaging, and beds for both groups; as well as the FFR catheter-related costs for the FFR group. The follow-up costs were comprised of the expenses of illness-related medications within 1 year after discharge and the costs of readmission.

The primary costs were compared between the FFR and control groups (Table 3). The average cost was significantly less in the FFR group than in the control group, even when the cost of the FFR catheter was considered (Table 3). The follow-up costs were also compared between the 2 groups (Table 4): the patients who underwent PCI paid an additional cost for clopidogrel on top of aspirin, resulting in a significant difference in the follow-up costs between the groups (Table 4).

Health utility and health-related quality of life: The utility of FFR and its role in improving the quality of life were investigated by using a VAS and the EQ-5D. QALY is an index that indicates the benefits or utility of an individual's health status and is defined as utility multiplied by years. A QALY value closer to 0 denotes a less favorable health status.

The utility rate was determined directly on the basis of the VAS method at the time of hospitalization for the index procedure. The mean of this value was 0.66 ± 0.1 in the control group and 0.64 ± 0.1 in the FFR group, indicating no significant difference (P = 0.232). At 1 year's follow-up, the QALY value was 0.7449 ± 0.10139 in the control group and 0.8643 ± 0.0961 in the FFR group, indicating that the health status was significantly better in the FFR group (P < 0.001) (Table 5).

Cost-effectiveness analysis: The total cost of diagnosis, treatment, and follow-up during the 1-year period in the FFR group was lower than that in the control group (35.7 ± 113 million rials vs 73.8 ± 158 million rials; $P < 0.001$). Moreover, the risk of complications was 2.5 times higher in the control group than in the FFR group. On the other hand, the effectiveness of the intervention in the FFR group was significantly higher than that in the control group. (QALY was 0.86 ± 0.1 after 1 year in the FFR group, as opposed to 0.75 ± 0.1 in the control group [$P < 0.001$].) Simply put, the cost-effectiveness ratio was 113 000,000/0.86 = 131 395 349 QALY/rials in the FFR group and 158 000 000/0.75 = 210 666 667 QALY/rials in the control group. Thus, after 1 year, QALY for each patient in the FFR and control groups cost about 131 million rials and about 210 million rials, respectively, clearly indicating the cost-effectiveness of FFR utilization for guiding PCI.

The cost of each QALY was determined through the division of the total cost by the amount of QALY in the first year (the utility rate at the end of the year minus the baseline utility rate: 0.86 − 0.64 = 0.23 in the FFR group and 0.75 − 0.66 = 0.09 in the control group). This amount was approximately 491 million rials (113 000 000/0.23) in the FFR group and 1755 million rials (158 000 000/0.09) in the control group. In other words, QALY of a year for each patient in the control group cost 3.3 times more than that for each patient in the FFR group, justifying once more the cost-effectiveness of FFR-guided PCI.

One of the indices used in the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER), defined as $\frac{(C1-C0)}{(E1-E0)}$, with C1 and E1 respectively representing cost and effectiveness in the FFR group and C0 and E0 correspondingly representing cost and effectiveness in the control group. The ICER was about:

$$ICER = \frac{|113,000,000 - 158,000,000|}{(0.86 - 0.75)} = 409,090,909\ /rials$$

In other words, a reduction in the costs of diagnosis, treatment, and follow-up for each unit of effectiveness was about 409 million rials in the FFR group. What is also of significance is that if the cost of the FFR catheter is deducted from the total cost, the cost will amount to 431 million rials. Consequently, the cost-effectiveness of the use of FFR was at least 409 million rials and at most 431 million rials for each QALY.

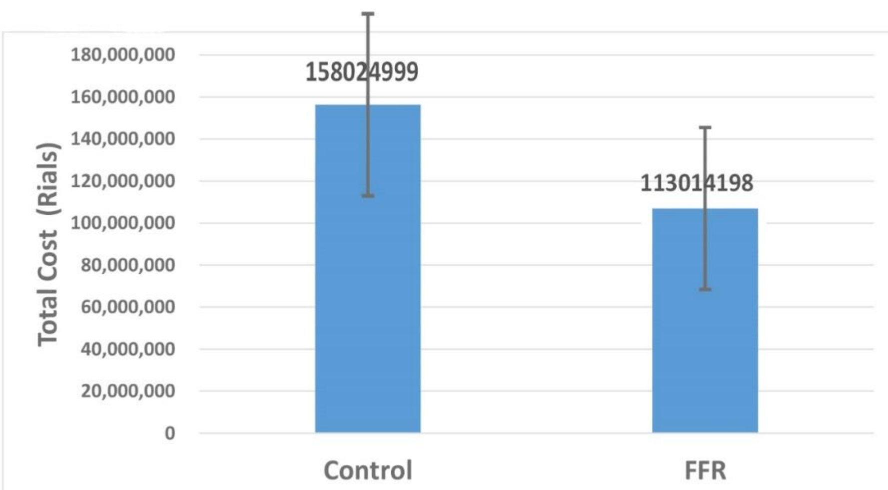


Figure 2: Comparisons of the total cost (the primary costs and the costs of the first year of follow-up) between the FFR and control group
FFR, Fractional flow reserve

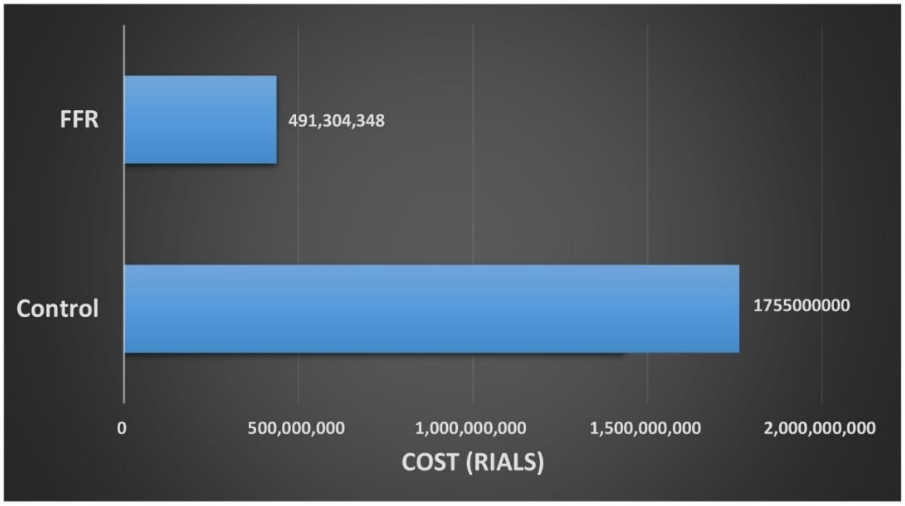


Figure 3: Comparisons of the cost-effectiveness of the FFR implementation between the 2 study groups
FFR, Fractional flow reserve

Table 5: Utility of the use of FFR based on QALY in the 2 groups

	Control (n=90)	FFR (n=98)	*P* value
Baseline utility	0.655 ± 0.09543	0.638 ± 0.09888	0.232
First-year QALY	0.7449 ± 0.10139	0.8643 ± 0.0961	<0.001
Gained QALY	0.0899 ± 0.13202	0.2263 ± 0.14958	<0.001

FFR, Fractional flow reserve; QALY, Quality-adjusted life-year

DISCUSSION

In the present study, we aimed to evaluate the cost-effectiveness of FFR in a cardiovascular tertiary center in Iran. FFR was cost-effective based on various indices in our study and importantly, the patients collected in the FFR group had significantly lower MACE and readmission rates.

Coronary angiography is the gold-standard diagnostic method for determining the severity of coronary artery stenosis. However, not only is the accuracy of coronary angiography diminished when it comes to a moderate lesion but also it is unable to define the functional significance of a lesion. [5] Notably, it has been demonstrated that reliance on anatomical involvement may render the superiority of revascularization over medical therapy questionable. [2] On the other hand, the specificity of noninvasive diagnostic modalities for analyzing coronary arterial segments separately is limited. [6,11] Since its introduction, FFR-guided PCI has proven to be safe and effective in decreasing unnecessary procedures, cardiac mortality, and hospitalization. [3] The method has also been superior to optimized medical therapy in reducing urgent revascularization. Despite the high-quality evidence and also strong guideline recommendations, the utilization of FFR is still limited, especially in developing countries. This situation is exacerbated by a lack of insurance coverage.

Our results revealed that FFR-guided PCI among our study population led to significantly lower MACE and rehospitalization rates at 1 year's follow-up, which could be due to the prevention of unnecessary stenting. The other endpoints such as mortality and myocardial infarction in our study were not similar between the 2 groups, probably because of the sample size. Our results are in concordance with various studies performed in this field. [3,8,12] A meta-analysis performed by Zhang et al [13] on nearly 50 000 patients confirmed the same observation. The meta-analysis showed that the decreased absolute risks of MACE/major adverse cardiac and cerebrovascular events, death, myocardial infarction, revascularization, and death or myocardial infarction for angiography-guided PCI and FFR-guided PCI were 34.8% vs 22.5%, 15.3% vs 7.6%, 8.1% vs 4.2%, 20.4% vs 14.8%, and 21.9% vs 11.8%, respectively.

In the present study, first and foremost, we showed that the QALY value was bettered in the FFR group by comparison with the control group (0.8643 ± 0.0961 vs 0.7449 ± 0.10139, respectively; *P* < 0.001), which resulted in a lower cost for each QALY in the FFR group compared with the control group (131 395 349 QALY/rials vs 210 666 667 QALY/rials, respectively; *P* < 0.001). In addition, we calculated the ICER index, which showed that the cost-effectiveness of FFR use was at least 409 million rials and at most 431 million rials for each QALY, depending on the inclusion of the cost of the FFR catheter.

Siebert et al [9] showed that FFR was cost-saving and diminished costs at 1 year's follow-up by 1776 Australian dollars per patient. They also expanded their analysis to 2 years and demonstrated a gained public health impact from 7.8 to 73.9 QALYs, which was translated to a budget impact of 1.8 to 14.5 million Australian dollars' total cost savings. The existing literature contains a few studies that have calculated the ICER for FFR-guided PCI. Quintella et al [5] showed an ICER index of 21 156.55 Brazilian reals in a Brazilian population for FFR-guided PCI, which is considered cost-effective.

The cost-benefit evaluations of the FAME study revealed that FFR-guided PCI in patients with multivessel coronary disease was one of those rare modalities in which a technology not only improves outcomes but also saves resources. [14,15]

The present study has several limitations. The observational nature of the study and attribute confounding factors might influence the final results. Additionally, the limited number of our studied population can impact the analysis.

CONCLUSIONS

The results of the current investigation demonstrated that FFR-guided PCI for moderate lesions in multivessel coronary artery disease was a precise and cost-effective method, conferring lower MACE and hospitalization rates. Our results might help insurance companies to incorporate FFR in their coverage.

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