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Percutaneous Coronary Intervention

The Impact of Fractional Flow Reserve-Guided Coronary Revascularization in Patients with Coronary Stenoses of Intermediate Severity

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Background: Previous studies have shown that the use of fractional flow reserve (FFR) in addition to angiography significantly reduced the rate of all major adverse cardiovascular events (MACE). However, this practice has not been widely accepted and limited outcome data exist about FFR-guided percutaneous coronary intervention (PCI) in Taiwan. The aim of the present study was to evaluate the possible impact of FFR-guided PCI in coronary stenoses of intermediate severity.

Methods: We performed a retrospective case-control study on 443 cases of intermediate coronary stenoses in 206 patients recruited from our computerized database. The study patients were divided into two groups: the FFR group (n = 101) and the angiography group (n = 105), matched with age, gender, clinical and angiographic lesion characteristics. In the angiography group, the indicated lesions had been treated with PCI by angiographic or anatomical assessment, whereas those patients in the FFR group underwent PCI of indicated lesions only if the FFR was < 0.80. The primary end point was the MACE rate regarding death, nonfatal myocardial infarction (MI), and target vessel failure at a mean follow-up of 418 days.

Results: The MACE rate was similar in both groups (6% in the angiography group and 3% in the FFR group, p = 0.06). However, FFR-guided PCI strategy prevented unnecessary revascularization in up to 75% of patients, and markedly reduced costs of the index hospitalization. Moreover, multivariate analysis found that the use of drug-eluting stent and statin therapy, and the presence of family history of premature coronary artery disease and periprocedural MI are independent predictors of clinical outcomes.

Conclusions: FFR-guided intervention, compared to angiography-guided intervention for Taiwanese patients with coronary stenoses of intermediate severity, achieved similar clinical outcomes and provided cost-savings.

Key Words: Coronary artery disease • Fractional flow reserve • Percutaneous coronary intervention • Prognosis

INTRODUCTION

Recent studies have demonstrated that ischemia-guided coronary revascularization may improve the clinical outcomes of stable coronary artery disease (CAD).[1-3] It is recommended that coronary revascularization should be performed only in cases with coronary stenoses that are ischemia-generating.[4-7]

The traditional method for determining the severity of coronary stenosis is coronary angiography. However, the visual assessment, or so-called "eyeball technique", of percent diameter reduction has significant inter-observer variability, even among experienced angiographers.[3,4,8] Over the last decade, profound clinical and

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scientific evaluation has demonstrated that fractional flow reserve (FFR) is one of the few diagnostic modalities that improve patient outcome while being cost-effective and cost-saving.[1,2,9-17]

The Taiwan National Health Insurance program began reimbursing FFR in 2012. The current Reimbursement Guidelines recommend measuring FFR before "ad hoc" percutaneous coronary intervention (PCI) for intermediate lesions (50-70% diameter stenosis). However, this practice is not widely accepted, and limited outcome data exist about changing PCI practice according to FFR guidance.

We hypothesized that an FFR-guided treatment strategy is associated with favorable clinical outcomes. In the present study, we performed a retrospective case-control study to evaluate the possible impact of FFR-guided PCI in coronary stenoses of intermediate severity.

METHODS

Study population

We studied 443 episodes of intermediate coronary stenoses in 206 patients. The patients were scheduled for possible PCI at the Cheng Hsin General Hospital between July 2012 and January 2014, and were recruited from our computerized database. The study patients were divided into two groups: the FFR group (101 patients, 224 lesions) and the angiography group (105 patients, 219 lesions).

For those patients who underwent FFR-guided PCI, the operator identified coronary lesions with a diameter stenosis of 50-70% that may require stenting. Patients initially had FFR measured in the diseased coronary artery, and only underwent stenting if the FFR value was < 0.80.

The 105 patients in the angiography group were randomly selected from a patient population of 426 patients for intermediate coronary stenoses by quantitative coronary angiography (QCA) during the concurrent period of time. The patients were matched with age, gender, risk factors, comorbidities, number of diseased vessel, target vessel, and angiographic lesion characteristics. In the angiography-guided PCI group, the decision-making of PCI for the intermediate coronary lesions was according to the angiographic or anatomical assessment, severity of stress tests (treadmill exercise test or thallium 201 scan) and the patients' wishes. Finally, a total of 95 patients had received angiography guided PCI.

The selection of patients was based on reviewing the patients' medical records and diagnostic angiograms by two physicians (H.L.J. and W.P.H.), who were blinded to the patients' procedural characteristics and clinical outcomes.

This retrospective study was approved by the local ethics committee; the informed consent requirement was waived because of the study's retrospective nature.

PCI procedure

All procedures were performed after written informed consents had been obtained. The choice between using a radial or a femoral artery approach was left to the discretion of the treating physicians. Six French guide catheters were the default strategy for TR procedures. In those patients who undergone femoral artery approach, 7/8 French guide catheters were used. All patients were preloaded with dual anti-platelet therapy, and all received intravenous unfractionated heparin (70 units/kg) during the procedure. For procedures lasting longer than 1 hour, activated clotting time was measured, aiming for 250 s. Glycoprotein IIb/IIIa inhibitor use was at the operator's discretion.

In those patients who underwent stenting, the stent length was chosen so as to cover the entire lesion, including the proximal and distal edges. In case of multiple stents, overlapping was performed. After stent deployment, post-dilatation for stent optimization under quantitative angiography and/or intravascular ultrasound guidance was performed if residual in-stent stenosis was ≥ 20% of the vessel diameter.

In patients who underwent transradial PCI, the radial artery sheath was removed immediately following completion of the procedure and hemostasis was achieved using a hemostatic bandage (Stepy®P, Nichiban Co. Ltd., Tokyo, Japan). For femoral procedures, the femoral sheath was left in place for 2-4 hours, until the activated clotting time was < 180 s. Adequate external compression and further gauze pressure dressings with sand bag compression were applied for at least 6 hours to achieve hemostasis. After the procedure, patients re-

ceived dual-antiplatelet therapy with clopidogrel (75 mg/day) and aspirin (100 mg/day) for at least 3 months if they had received a bare metal stent, and 12 months if they had received a drug-eluting stent (DES).

Study definitions

Coronary lesions were classified according to guidelines of the ACC/AHA Task Force on percutaneous transluminal coronary angioplasty. Procedural success was defined as having achieved a grade 3 thrombolysis in myocardial infarction (TIMI) flow and reduction of the target lesion to < 20% luminal diameter by visual angiographic assessment in the absence of mortality, myocardial infarction (MI) or stent thrombosis. Bleeding was classified as minor or major, depending on whether the bleeding was associated with hemodynamic compromise and/or blood transfusion. Vascular access site referred to any arterial or venous puncture site used for the procedure. Deaths were classified as either cardiac or non-cardiac; if death resulted from unascertained causes, it was categorized as cardiac. Periprocedural MI was defined as new Q waves or as creatine kinase-MB (CK-MB) greater than 3 times the upper limit of normal within 24 hours of PCI, along with an increase of 50% above the most recent pre-PCI level.[18] Small vessel meant reference vessel diameter of the target lesion ≤ 2.5 mm. Small vessel disease was referred to as the presence of the luminal diameter ≤ 2.5 mm in all segments of the major coronary arteries [left anterior descending artery (LAD) or left circumflex artery (LCX) or right coronary artery (RCA)]. Diffuse lesion represented lesion length ≥ 30 mm. Calcified lesion was defined as any faint or dense radiopacities noted during the dynamic image of cardiac cycles or without cardiac motion before contrast injection.[19]

Besides, it is generally understood that stenting performed in reference vessel diameter ≥ 3.0 mm typically has a better outcome, compared with smaller vessel stenting.[20] Therefore, smaller lesion size in our study (Table 4) represented target lesion stent diameter < 3.0 mm.

Post-procedural biomarkers were measured routinely, at 6 hours and 12 hours after the index procedure. Target vessel failure (TVF) was defined as the need for a new revascularization, either percutaneous or surgical, of the vessel previously treated and was clinically driven. Major adverse cardiovascular events (MACE) included death, recurrent non-fatal MI, and TVF. Acute stent thrombosis was classified according to the Academic Research Consortium criteria. The primary outcome measure was defined as total MACE rates at the end of the follow-up period of July 2015.

FFR measurements[21]

The FFR is defined as the ratio between distal coronary pressure and aortic pressure, both measured simultaneously at maximal hyperemia. Distal coronary pressure was measured with a coronary pressure guidewire (Certus Pressure Wire, St. Jude Medical, St. Paul, Minnesota, USA). Intra-coronary (I.C.) bolus injection of adenosine at a dosage of 150 μg was given and followed by rapidly flushing with saline solution then FFR, after which arterial blood pressure (BP) and heart rate (HR) readings were recorded after 3 seconds. HR and BP were recorded in order to indicate the hyperemic state, evidenced by a 10-20% decrease in BP and a similar increase in HR. If maximal hyperemia could not be achieved, increasing the doses incrementally by 50 μg to a maximum of 300 μg, depending on the dose response. As aforementioned, only those patients with FFR value of < 0.8 measured in the diseased coronary artery underwent PCI.

Data collection and patient follow-up

In the present study, all data were retrospectively collected by trained research assistants and taken from our computerized database in a preplanned analysis. A total of 101 consecutive patients with intermediate coronary stenoses, who had undergone diagnostic angiographic and FFR evaluation for possible PCI from July 2012 to January 2014 were recruited as the FFR group. The other 105 patients who had undergone angiography study for possible PCI during the same period were retrospectively selected and served as the control (angiography group).

Baseline characteristics, such as risk factors, co-morbidities, clinical presentation, left ventricular ejection fraction (by echocardiography), angiographic and procedural characteristics, blood biochemistry as initial and follow-up plasma CK, CK-MB, and cardiac troponin I levels, and medications at discharge, were collected from medical records.

Clinical follow-up was conducted based on medical records from the computer database, and telephone

contacts for at least 6 months after the index PCI procedure for each patient.

Statistical analysis

Categorical variables are expressed as proportions, and continuous variables are expressed as mean ± SD. Univariate comparisons of clinical characteristics and laboratory measurements between these groups were made with the Student's t-test or the Mann-Whitney U test for quantitative data, and with the Chi-square test or Fisher's exact test for qualitative data.

Logistic regression was used to determine the major determinants of significant myocardial ischemia (a FFR < 0.8). Linear regression analysis was used to determine the correlation between the reference vessel diameters and FFR. In multivariable Cox proportional hazards analyses, the predictors of clinical outcomes during follow-up were identified.

All values are 2-tailed, and a p value < 0.05, considered statistically significant.

The statistical software package SPSS version 12.0 (SPSS Inc) was used for all analyses.

RESULTS

Baseline clinical characteristics (Table 1)

The baseline demographic and clinical characteristics of both FFR group and angiography group are shown in Table 1. The two treatment groups were similar with regard to age, gender, risk factors, comorbidities, Canadian Cardiac Society angina class, and left ventricular ejection fraction. But significantly more patients in the angiography group were on statin therapy (90 vs. 52%, p < 0.001), and had P2Y12 inhibitor administrated (91% vs. 31%, p < 0.001) at discharge due to coronary artery stenting.

Angiographic characteristics (Table 2)

We recruited patients with 443 lesions, matched with angiographic lesion characteristics, from our computerized database. Table 2 lists the angiographic characteristics in both groups in this study. All of the 443 lesions were de novo lesions. The two treatment groups were similar with regard to the number of diseased vessel, target vessel treated, Syntax score, lesion size, and lesion length, except for the percentage of patients underwent PCI procedure was significantly higher in the angiography-guided PCI group compared to the FFR-guided PCI group (90% vs. 25%, p < 0.001).

Procedural characteristics (Table 3)

One-hundred and nine of the total 120 (91%) PCI patients in the two groups underwent stent implantation following pre-dilatation with a conventional balloon or a cutting balloon, or rotablation. Among them, 98/109 (90%) underwent stenting with a DES. The mean stent diameter and stent length were similar in both groups. The two treatment groups were similar with regard to other procedural characteristics, including the use of drug-eluting balloon, intravascular ultrasound, or debulking technique. In the FFR group, successful PCI

Table 1. Baseline clinical characteristics of the study patients

Parameter	Angiography group (N = 105)	FFR group (N = 101)	p value
Age, years	61 ± 11	66 ± 9	0.720
Male, n (%)	82 (78%)	74 (73%)	0.604
Family history of CAD, n (%)	27 (26%)	32 (32%)	0.926
Hypertension, n (%)	72 (69%)	76 (75%)	0.800
Dyslipidemia, n (%)	85 (81%)	92 (91%)	0.696
Diabetes mellitus, n (%)	39 (37%)	35 (35%)	0.882
CKD, stage ≥ 3	21 (20%)	28 (28%)	0.352
PAOD, n (%)	8 (7%)	1 (1%)	0.115
Previous stroke or TIA, n (%)	8 (7%)	4 (4%)	0.234
Previous MI, n (%)	23 (22%)	15 (15%)	0.411
Angina, CCS class			
II, n (%)	75 (71%)	85 (84%)	0.557
III, n (%)	21 (20%)	11 (11%)	0.213
IV, n (%)	9 (9%)	5 (5%)	0.179
LVEF < 50%, n (%)	16 (15%)	9 (9%)	0.367
Medications, at discharge			
Aspirin, n (%)	88 (84%)	74 (73%)	0.734
P2Y12 inhibitor*, n (%)	96 (91%)	31 (31%)	< 0.001
Beta-blocker, n (%)	43 (41%)	35 (34%)	0.674
Calcium blocker, n (%)	48 (46%)	56 (55%)	0.614
Nitrate, n (%)	44 (42%)	33 (32%)	0.311
Statin, n (%)	95 (90%)	54 (52%)	< 0.001
ACEI/ARB, n (%)	51 (48%)	57 (56%)	0.308

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CAD, coronary artery disease; CCS, Canadian Cardiac Society; CKD, chronic kidney disease; FFR, fractional flow reserve; LVEF, left ventricle ejection fraction; MI, myocardial infarction; PAOD, peripheral artery occlusive disease; TIA, transient ischemic attack.

* Including Clopidogrel or Ticlopidine or Ticagrelor.

Table 2. Angiographic findings of the study patients

Parameter	Angiography group (N = 105)	FFR group (N = 101)	p value
Total lesions	219	224	0.545
Number of diseased vessel			
1-vessel disease, n (%)	33 (31%)	28 (28%)	0.690
2-vessel disease, n (%)	30 (29%)	23 (23%)	0.401
3-vessel disease, n (%)	42 (40%)	50 (49%)	0.404
Target vessel			
LAD, n (%)	55 (52%)	64 (63%)	0.122
LCX, n (%)	26 (25%)	20 (20%)	0.369
RCA, n (%)	24 (23%)	17 (17%)	0.230
Syntax score	11.98 ± 6.77	12.02 ± 6.24	0.162
Lesion characteristics			
Lesion type A, n (%)	17 (16%)	20 (20%)	0.349
Lesion type B, n (%)	85 (81%)	79 (78%)	0.714
Lesion type C, n (%)	3 (3%)	2 (2%)	0.250
Ref. vessel diameter, mm	2.97 ± 0.41	2.80 ± 0.54	0.764
Diameter stenosis			
51-60% stenosis	24 (23%)	29 (29%)	0.464
61-70% stenosis	81 (77%)	72 (71%)	0.620
Bifurcation lesion, n (%)	23 (22%)	16 (16%)	0.343
Small vessel, n (%)	34 (32%)	40 (40%)	0.420
Diffuse lesion, n (%)	30 (24%)	16 (16%)	0.324
Calcific lesion, n (%)	39 (37%)	30 (30%)	0.439
PCI rate, n (%)	95 (90%)	25 (25%)	< 0.001

Calcified lesion, any faint or dense radiopacities noted during the dynamic image of cardiac cycles or without cardiac motion before contrast injection; Diffuse lesion, lesion length ≥ 30 mm; FFR, fractional flow reserve; LAD, left anterior descending artery; LCX, left circumflex artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; Ref. vessel diameter, reference vessel diameter; Small vessel, reference vessel diameter ≤ 2.5 mm.

procedures could significantly improve the FFR values (post-PCI FFR vs. baseline FFR: 0.90 ± 0.06 vs. 0.76 ± 0.04; p < 0.001).

Although the stenting rate and the use of DES in those patients who underwent PCI were similar in both groups (angiography-guided PCI group vs. FFR-guided PCI group: 92% vs. 88%, p = NS and 82% vs. 80%, p = NS), the total number of stents used was significantly lower in the FFR group as compared to the angiography group (angiography group vs. FFR group: 121 pieces vs. 27 pieces, p < 0.001). Furthermore, the mean cost of the index hospitalization per patient was also significantly lower in the FFR group, compared to that of the angiography group (NT$ 63,991 ± 16,781 vs. 107,578 ± 42,791; p < 0.001).

The incidences of PCI procedure-related complications are significantly higher in the angiography-guided PCI group. The incidence of periprocedural MI was significantly highly in the angiography-guided PCI group, compared to those of the FFR-guided PCI group (18% vs. 4% p < 0.001).

Logistic regression to identify predictors of patients with significant ischemia using FFR

According to logistic regression analysis (Table 4),

Table 3. Cost of patient hospitalization and PCI procedural characteristics

Parameters	Angiography group (n = 105)	FFR group (n = 101)	p value
Cost of the index hospitalization, NT$	107,578 ± 42,791	63,991 ± 16,781	< 0.001
Number of stents per patient (%)	1.2 ± 0.6	0.3 ± 0.4	< 0.001
Parameters	**Angiography-guided PCI group (n = 95)**	**FFR-guided PCI group (n = 25)**	**p value**
Stenting, n (%)	87 (92%)	22 (88%)	0.325
Drug-eluting stent, n (%)	78 (82%)	20 (80%)	0.961
Bare-metal stent, n (%)	6 (6%)	1 (4%)	0.322
Stent diameter, mm	2.98 ± 0.49	2.83 ± 0.57	0.626
Stent length, mm	29.52 ± 9.44	19.90 ± 6.97	0.004
Balloon angioplasty only, n (%)	8 (8%)	3 (12%)	0.251
Cutting balloon, n (%)	5 (5%)	1 (4%)	0.329
IVUS, n (%)	7 (7%)	1 (4%)	0.093
Debulking, n (%)	7 (7%)	1 (4%)	0.093
FFR (before)	NA	0.76 ± 0.04	
FFR (after)	NA	0.90 ± 0.06	
PCI procedural complications			
Periprocedural MI, n (%)	17 (18%)	1 (4%)	< 0.001
Acute ST, n (%)	0 (0%)	0 (0%)	-
Periprocedural stroke, n (%)	0 (0%)	0 (0%)	-
Emergency operation, n (%)	0 (0%)	0 (0%)	-
Emergency CABG, n (%)	0 (0%)	0 (0%)	-
Major bleeding, n(%)	0 (0%)	0 (0%)	-

CABG, coronary artery bypass grafting; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MI, myocardial infarction; NT$, New Taiwan dollars; PCI, percutaneous coronary intervention; Periprocedure MI, new Q waves or as CK-MB greater than 3 times the upper limit of normal within 24 hours of PCI along with an increase of 50% above the most recent pre-PCI level; ST, stent thrombosis.

diabetes mellitus [hazard ratio (HR) = 7.289, 95% confidence interval (CI) = 1.047-50.48, p = 0.045], smaller reference vessel size (HR = 24.40, 95% CI = 2.102-283.2, p = 0.011), small vessel disease (HR = 18.08, 95% CI = 4.785-155.3, p < 0.001), and diffuse lesion (HR = 3.622 95% CI = 1.422-130.49, p = 0.023) are four independent positive predictors for the presence of significant ischemia, i.e., a FFR < 0.8. However, multiple vessel disease, calcified lesion, and history of MI were not risk factors of significant ischemia using FFR.

Clinical outcomes during follow-up

In our study, the mean follow-up duration in angiography group vs. FFR group was 431.7 ± 161.5 days vs. 407.2 ± 178.6 days, respectively (p = NS). No difference was shown regarding total MACE rates, and incidences of cardiovascular (CV) death, non-CV death, recurrent non-fatal MI, and TVF during follow-up (Table 5). But there was one patient with CV death in the FFR group. The patient had severe aortic stenosis and then received coronary angiograph study, which FFR showed to be insignificant ischemia (FFR > 0.8) and thus PCI was not performed. Finally, the patient refused aortic valve replacement therapy. Unfortunately, about 9 months later, he died of sudden onset of cardiac collapse.

By Cox proportional hazard analysis, the use of DES (HR = 0.078, 95% CI = 0.011-0.476, p = 0.015) and statin therapy (HR = 0.059, 95% CI = 0.013-0.776, p = 0.025) have beneficial effect on clinical outcomes. On the contrary, the presence of family history of early CAD (HR = 21.03, 95% CI = 1.087-198.6, p = 0.029) and periprocedural MI (HR = 31.72, 95% CI = 1.958-356.8, p = 0.017) are predictors of adverse events (Table 6).

Table 4. Predictors of significant ischemia (FFR < 0.8) by logistic regression in the FFR group (N = 101)

Parameters	Hazard ratio	95% C.I.	p value
Diabetes mellitus	7.289	1.047-50.48	0.045
Smaller lesion size	24.40	2.102-283.2	0.011
Small vessel disease	18.08	4.785-155.3	< 0.001
Diffuse lesion	3.622	1.422-130.49	0.023
Multiple vessel disease	1.153	0.752-1.768	0.514
Calcified lesion	1.395	0.502-3.876	0.523
History of MI	1.526	0.436-5.334	0.508

C.I., confidence interval; Calcified lesion, any faint or dense radiopacities noted during the dynamic image of cardiac cycles or without cardiac motion before contrast injection; Diffuse lesions, lesion length ≥ 30 mm lesion; FFR, fractional flow reserve; Smaller lesion size, target lesion stent diameter < 3.0 mm; Small vessel disease, the presence of the luminal diameter ≤ 2.5 mm in all segments of the major coronary arteries (LAD or LCX or RCA).

DISCUSSIONS

In this retrospective case-control study of real-world

Table 6. Predictors of major adverse cardiac events in the whole study cohort (N = 206)

Parameters	Hazard ratio	95% C.I.	p value
EuroScore	0.981	0.352-3.677	0.681
Syntax score	1.981	0.811-2.175	0.547
Diabetes mellitus	4.675	0.891-43.21	0.253
Statin use, at discharge	0.059	0.013-0.776	0.034
Family history of CAD	21.03	1.087-198.6	0.029
Drug-eluting stent	0.078	0.011-0.476	0.015
Periprocedural MI	31.72	1.958-356.8	0.017

CAD, coronary artery disease; C.I., confidence interval; MI, myocardial infarction.

Table 5. Clinical outcomes of the patients during follow-up

Parameters	Angiography group (N = 105)	FFR group (N = 101)	p value
Follow-up period, days	431.7 ± 161.5	407.2 ± 178.6	0.748
Total MACE, n (%)	6 (6%)	3 (3%)	0.061
CV death, n (%)	0 (0%)	1 (1%)	0.072
Non-CV death, n (%)	1 (1%)	1 (1%)	1
Non-fatal stroke, n (%)	0 (0%)	0 (0%)	-
Non-fatal MI, n (%)	1 (1%)	0 (0%)	0.072
Late/very late ST, n (%)	0 (0%)	0 (0%)	-
Target vessel failure, n (%)	3 (3%)	1 (1%)	0.051

CV, cardiovascular; FFR, fractional flow reserve; MACE, major adverse cardiovascular events; MI, myocardial infarction; ST, stent thrombosis.

practice in Taiwanese patients underwent PCI for intermediate stenotic lesions, FFR-guided strategy identifies those who can be treated conservatively with comparable clinical outcomes as the traditional angiography-guided PCI, and prevents unnecessary PCI. In doing so, FFR-guided strategy can not only reduce incidence of procedural complications, mainly periprocedural MI, but also reduce the medical expenditure of index hospitalization significantly.

In experimental models, it is accepted that a reduction of more than 70% of the cross-section of a blood vessel (i.e., 50% stenosis by diameter) is necessary to reduce coronary blood flow to an extent capable of inducing ischemia during exercise. This has been extrapolated to clinical practice, where a luminal stenosis of ≥ 50% (i.e., cross-section stenosis ≥ 70%) is now generally accepted as being significant because of its theoretical potential to cause ischemia.[22] The standards of PCI services payments of Taiwan National Health Insurance are consistent with the theory. In Taiwan, therefore, PCI may be performed routinely when coronary arterial cross-section stenosis ≥ 70% (i.e. diameter stenosis ≥ 50%).

An intermediate coronary lesion on angiography is defined as luminal narrowing with a diameter stenosis ≥ 50% but ≤ 70%.[23] The Taiwan National Health Insurance started to reimburse FFR beginning in 2012, and the current Reimbursement Guidelines recommend measuring FFR before "ad hoc" PCI for intermediate lesions (i.e. 50-70% diameter stenosis). However, this practice is not widely accepted in Taiwan and outcome data about changing PCI practice according to FFR guidance are lacking. So we perform this retrospective case-control study to evaluate the possible impact of FFR-guided PCI in coronary stenoses of intermediate severity in Taiwanese patients.

Our data clearly demonstrated that measurement of FFR in patients with CAD and borderline lesions prevents unnecessary revascularization procedures in up to 75% of cases, and has been proven to bring considerably more benefits, such as reducing procedural complications, without compromising event-free survival up to a mean follow up of 418 days. It is consistent with the findings of the DEFER study (FFR to determine the appropriateness of angioplasty in moderate coronary stenoses).[9] Actually, the incidence of periprocedural MI was significantly highly in the angiography-guided PCI group, compared to those of the patients in FFR-guided PCI group (18% vs. 4% $p < 0.001$). In the Cox proportional hazard analysis, periprocedural MI was identified as an important predictor of adverse clinical outcomes. In sum, the assumption that 'prophylactic' PCI of a stenotic lesion not inducing ischemia is beneficial overall and mustbe considered a misconception.

Another important finding of the study was that the averaged hospital cost of the index hospitalization was also significantly reduced in the FFR group, compared to that of the angiography group (NT$ 63,991 ± 16,781 vs. 107,578 ± 42,791; $p < 0.001$). According to the economic evaluation of the FAME study,[10] performing PCI guided by FFR in patients with multivessel CAD saves healthcare resources and improves health outcomes at 1-year compared with a traditional strategy of angiographic guidance. The cost savings occur both at the index procedure, primarily owing to a decrease in DES use being a major cost driver, which more than offsets the increased cost of the pressure wire and adenosine, and during follow-up as a result of a decrease in re-hospitalization and fewer MACE. About 90% of the total cost occurred at the index hospitalization. However, around 30% of the overall cost difference between the 2 strategies is generated during follow-up, indicating increasing cost savings even after the initial procedure.[17] Although we did not include in the costs generated during follow-up in our analysis, we did showed that the hospital costs of the index hospitalization were remarkably reduced in the FFR group, mainly driven by a decrease in DES use, unnecessary procedures, and length of stay in the hospital. Considering that cost-effectiveness is a "moving target", and lower acquisition costs of DES, availability of new devices that further reduce revascularization, and development of noninvasive FFR testing may all change the equation. Taking our study as an example, if we adopt FFR-guided PCI as a routine strategy for 100 patients with moderate coronary stenotic disease, only 25 of them would really need to undergo PCI. Although additional costs are needed for routine FFR measurement, the strategy will save 75 PCI procedures and shorten the length of stay of those patients. This may have major impacts on the quality of care in CAD patients and healthcare policy-making.

In our study, we also found that patients with diabetes mellitus and smaller reference vascular diameter are more likely to have lower FFR, and some smaller vessels with an intermediate stenosis and an FFR of < 0.8 supplying a significant territory of muscle should be considered clinically significant and therefore justified to be treated. This finding is clinically relevant because diabetic patients usually have diffuse atherosclerosis and are prone to have small vessel disease. It is known that stent implantation results in arterial injury, initiating a vasculo proliferative cascade with smooth muscle cell proliferation and migration resulting in neointimal hyperplasia.[24,25] The amount of neointimal hyperplasia is largely independent of vessel size, and thus, late luminal loss, an angiographic measure of neointimal hyperplasia, is similar across a wide range of vessel diameters.[24,25] Also, small vessels are more prone to restenosis than larger vessels because they are less able to accommodate neointimal tissue without compromising blood flow.[24,25] Although the correlation between anatomic measurements of intermediate coronary lesions obtained by intravascular ultrasound and FFR was better for larger-diameter vessels, it is recommended that vessel size should always be taken into account when determining the anatomic measurement associated with functional ischemia.[26] However, Puymirat et al. reported that long-term clinical outcome after FFR-guided PCI in patients with small-vessel disease shows that an FFR-guided PCI strategy in small artery stenosis is safe and results in better clinical outcomes as compared with angiography-guided PCI strategy.[27] Therefore, based on the current data, it should lead to more FFR utilization in stable, intermediate-severity lesions, especially in diabetic patients and those who have small vessel disease, so as to decide whether or not to treat patients with PCI. This approach can improve patient outcome and is, at the same time, cost-effective and cost-saving.

The present study had some limitations. Firstly, as we mentioned before, the main limitation of the present study was its retrospective nature. Smaller differences and confounders may exist between two groups, and may affect the success of either approach if examined in a prospective randomized manner. Certain degrees of the operators' biases based on their experiences with FFR measurements and FFR-guided PCI cannot be eliminated thoroughly either. Actually, FFR was performed at the discretion of the treating physicians. So they were not performed in a random manner. The possibility of selection bias cannot be excluded. Secondly, the small poll and short follow-up duration of the study has certainly reduced the power to detect significant differences. Thirdly, the absence of angiographic follow-up may underestimate the event rates. Nevertheless, there were no adverse trends in the FFR-guided PCI group. Fourthly, it is worth-noting that the present study was performed by those operators having substantial PCI experiences, so no major technical limitations would pose problems in their PCI; even so, the FFR-guided strategy can still reduce periprocedural MI and MN significantly. In other words, the benefits of FFR-guided PCI strategy may be more apparent with inexperienced operators as compared to angiography-guided PCI strategy. Besides, according to the previous studies,[28,29] lesion length is relevant to the assessment of the physiological significance of intermediate-grade coronary lesions. But in our computerized database, there were no data to assess the lesion length, so we cannot provide the relationship of lesion lengths and FFR values in the study. However, we found the diffuse lesion (> 30 mm) (HR = 3.622, 95% CI = 1.422-130.49, p = 0.023) was a risk factor of significant ischemia (FFR < 0.8) by logistic regression analysis in the FFR group (Table 4). Finally, in the FAME study, routine measurement of FFR in patients with multivessel coronary artery disease significantly reduces the rate of the composite end point of death, nonfatal MI, and repeats revascularization at one year.[10] But in our study, it cannot show the better clinical outcomes. It may be due to our smaller sample size and relatively lesser degree of severity of the intermediate coronary artery diseases compared with the FAME study.

CONCLUSIONS

FFR can provide real-time measurement of the extent to which a given epicardial stenosis limits maximal myocardial flow. FFR-guided intervention, compared to angiography-guided routine intervention for Taiwanese patients with coronary stenoses of intermediate severity, achieved similar clinical outcomes and provided cost-saving benefits.

CONFLICT OF INTEREST

None declared.

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