Comparison of clinical outcome after revascularization versus conservative treatment in patients with borderline fractional flow reserve measurements

by

Kyoung Woo Seo

Major in Medicine

Department of Medical Science

The Graduate School, Ajou University

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Kyoung Woo Seo

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Supervised by

Seung Jea Tahk, M.D., Ph.D.

Major in Medicine

Department of Medical Science

The Graduate School, Ajou University

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This certifies that the dissertation

of Kyoung Woo Seo is approved.

SUPERVISORY COMMITTEE

Seung Jea Tahk

Seung Jea Tahk

Joon Han Shin

Joon Han Shin

Hong Seok Lim

Hong Seok Lim

The Graduate School, Ajou University

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- ABSTRACT -

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Background: Measurement of fractional flow reserve (FFR) is useful tool for assessing the functional severity of coronary artery stenosis and for clinical decision of treatment strategy. Many studies have shown that FFR measurement <0.75 is specific for ischemia, but there is a controversy about whether we need to intervene the lesion of FFR measurement 0.75-0.80 or not. The objective of this study is to compare the clinical outcomes of revascularization versus conservative treatment in the borderline FFR measurement lesions.

Methods: We used the FFR-Registry database out of 4 centers in Korea. In 267 patients (mean age 62 ± 10 years, male 69%), 277 lesions (LAD, 213; LCX, 40; RCA, 24) with FFR measurement between 0.75 and 0.80 (mean 0.77±0.02) were included in this study. The rate of major adverse cardiac events (MACE; death, myocardial infarction, target lesion revascularization) and target lesion related events (TLRE; FFR-evaluated lesion revascularization, FFR-evaluated lesion-related myocardial infarction) were evaluated at 1 year follow up. Sixty-seven lesions from 66 patients were deferred from revascularization (Conservative group) and 210 lesions from 201 patients were treated with percutaneous coronary intervention (PCI group).

Results: For 1 year follow-up, 4 cases of TLRE (4 cases of FFR-evaluated lesion revascularization and no case of FFR-evaluated lesion-related myocardial infarction) from 4 patients occurred in the Conservative group and 8 cases of TLRE (8 cases of FFR-evaluated lesion revascularization and 1 case of FFR-evaluated lesion-related myocardial infarction) from 8 patients occurred in the PCI group.

Five cases of MACE (1 case of death, no case of myocardial infarction and 5 cases of target lesion revascularization) occurred in the Conservative group and 13 cases of MACE (4 cases of death, 2 cases of myocardial infarction and 9 cases of target lesion revascularization) occurred in the PCI group.

Using Cox proportional hazard model, there was no difference in lesion-related events between Conservative-group and PCI-group (hazard ratio 0.303, 95% CI 0.5-2.025, P = 0.218).

Conclusions: In coronary lesions with borderline FFR, revascularization did not show the better clinical outcome compared to medical treatment. Therefore, lesions with borderline FFR measurement can be deferred from revascularization without an increased risk for lesion-related outcomes.

Keyword: fractional flow reserve, coronary artery disease, percutaneous coronary intervention, medical treatment

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I. INTRODUCTION

Coronary artery disease can be treated with balloon or coronary stent for improvement of symptom and clinical outcome. For these purposes, we need to find the lesion inducing ischemia and to intervene only these lesions. Measurement of fractional flow reserve (FFR) is useful tool for assessing the functional severity of coronary artery stenosis and for clinical decision of treatment strategy (Kern et al., 2006). Using FFR seems to be necessary during coronary angiography in multivessel coronary artery disease patients (Tonino et al., 2009). Many studies have shown that FFR measurement <0.75 is specific for ischemia and lesions with FFR measurement > 0.8 is not inducing ischemia (Pijls et al., 1995; Pijls et al., 1996; Abe et al., 2000; Kern, 2000; Chamuleau et al., 2001; Tonino et al., 2009). There are several studies used the cutoff value as FFR measurement of 0.8, but there still is a controversy about whether we need to intervene the lesion of FFR measurement 0.75-0.80 or not. Further studies are needed for making decision for the lesions with 'gray zone' FFR measurements.

The objective of this study is to compare the clinical outcomes of revascularization versus conservative treatment in the borderline FFR measurement lesions.

II. Method

A. Patient population

We used the multicenter registry database out of 4 centers in Korea. In each hospital, patients who had at least one lesion underwent an FFR measurement during coronary angiography were enrolled. We excluded patients with significant left main disease, in-stent restenosis, acute myocardial infarction and graft vessel disease.

B. Procedure and treatment

Coronary angiography was performed following technique after intracoronary administration of 100 to 200μg nitroglycerin (NTG). Quantitative coronary angiography (QCA) analysis was performed using the Cardiovascular Angiography Analysis System II (CAAS II, Pie Medical, Maastricht, Netherlands).

FFR was measured with a 0.014-in pressure wire (St. Jude Medical System, Uppsala, Sweden). After passing the pressure wire through the lesion, distal coronary pressure (Pd) and proximal coronary pressure (Pa) were measured at baseline and maximal hyperemia. FFR was calculated by dividing mean Pd by mean Pa during maximal hyperemia. Maximal hyperemia was induced with an intracoronary bolus administration (80μg in left coronary artery, 40μg in right coronary artery), intracoronary (240-420μg/min) or intravenous continuous infusion (140μg/kg/min) of adenosine (De Bruyne et al., 2003; Yoon et al., 2009; Seo et al., 2012). The route of adenosine administration was depended on the operator's discretion.

The Patients who had borderline FFR > 0.75 and < 0.80 were categorized into the Conservative group (medical treatment) and the percutaneous coronary intervention (PCI) group (intervention with balloon or stent) according to the treatment strategy.

C. Follow up and endpoints

In all patients, clinical follow-up data were obtained from clinic visit or phone contact and collected through a web case reporting form. Clinical outcomes included target lesion related events (TLRE), target lesion failures (TLF) and major adverse cardiac events (MACE) at 1

year. Primary endpoint was TLRF at 1 year and secondary endpoints were TLF and MACE at 1 year.

Target lesion related events were defined as FFR-evaluated lesion revascularization and FFR-evaluated lesion related myocardial infarction. Target lesion failures were defined as cardiac death, FFR-evaluated vessel myocardial infarction, FFR-evaluated lesion revascularization. And MACE included death, myocardial infarction, FFR-evaluated lesion revascularization. Through these three outcome categories, we had intended to evaluate both lesion specific outcome and patient specific outcome. The study protocol was approved by the Institutional Review Board at each participating center.

D. **Statistical analysis**

Categorical variables are presented as frequencies and percentages. Categorical variables were compared using chi-square tests or Fisher's exact tests. Continuous variables are presented as mean ± SD. Independent t test or paired t test were used to compare the continuous variables between the 2 groups. A p value of < 0.05 was considered statistically significant for the comparison between the two groups. SPSS version 18.0 was used for data analysis. The times to event data were presented as Cox proportional hazard model was used to compare the clinical outcome of both groups.

III. Results

A. **Baseline characteristics**

A total of 267patients and their 277 lesions were eligible and enrolled to the study. Baseline characteristics of patients and lesions are shown in Table 1 and 2. Sixty-seven lesions from 66 patients were deferred from revascularization (Conservative group) and 210 lesions from 201 patients were treated with PCI (PCI group).

Patients in the conservative group were more likely to be older (64.5±9.6 years old vs. 61.6±9.7 years old, p=0.038), to have higher LV ejection fraction (63.4±8.2% vs. 60.2±8.0%, p=0.011) and to have more multi-vessel disease (77.3% vs. 58.7%, p=0.007) compared with those in the PCI group. There was inhomogeneous distribution of the target vessels (p=0.027) with more non-LAD lesions in the conservative group.

In patients treated with PCI, the mean FFR was lower (0.78±0.02 vs. 0.77±0.02, p<0.001) with more severe diameter stenosis by angiograph (58.1±11.5% vs. 52.2±12.7%, p=0.001) and reference diameter was bigger (3.00±0.44mm vs. 2.85±0.56, p=0.035) compared to the conservative group.

Table 1. Baseline clinical characteristics of the patients (n=267)

Characteristics	Conservative group (n=66)	PCI group (n=201)	p value
Age	64.5 ± 9.6	61.6 ± 9.7	0.038
Male	44 (66.7%)	140 (69.7%)	0.649
Hypertension	47 (71.2%)	127 (63.2%)	0.235
Diabetes mellitus	23 (34.8%)	73 (36.3%)	0.829
Smoking	15 (22.7%)	36 (17.9%)	0.388
Dyslipidemia	29 (43.9%)	74 (36.8%)	0.302
LV EF (%)	60.2 ± 8.0	63.4 ± 8.2	0.011
Clinical presentation			0.701
Stable angina	41 (62.1%)	113 (56.2%)	
Unstable angina	17 (25.8%)	60 (29.9%)	
Silent ischemia	8 (12.1%)	28 (13.9%)	
Previous MI	5 (7.6%)	8 (4.0%)	0.239
Previous PCI or CABG	11 (16.7%)	32 (15.9%)	0.886
CAD			0.017
One vessel disease	15 (22.7%)	83 (41.3%)	
Two vessel disease	26 (39.4%)	68 (33.8%)	
Three vessel disease	25 (37.9%)	50 (24.9%)	
Average follow-up(months)	30.3 ± 21.6	32.5 ± 21.2	0.470
Medication at discharge			
Aspirin	64 (97.0%)	200 (99.5%)	0.152
Beta blocker	28 (42.4%)	97 (48.5%)	0.410
ACEi/ARB	28 (42.4%)	86 (42.8%)	0.959
Lipid lowering agent	52 (78.8%)	152 (75.6%)	0.599
Anti-angina	52 (78.8%)	156 (77.6%)	0.842

Values are mean ± SD or n (%); PCI, percutaneous coronary intervention; LV, left ventricular; EF, ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; CAD, coronary artery disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Table 2. Angiographic and procedural results

	Conservative lesions (n=67)	PCI lesions (n=210)	p value
Lesion Location			0.027
LAD	50 (74.6%)	163 (77.6%)	
LCX	15 (22.4%)	25 (11.9%)	
RCA	2 (3.0%)	22 (10.5%)	
FFR value	0.78 ± 0.02	0.77 ± 0.02	<0.001
Minimal lumen Diameter (mm)	1.35 ± 0.36	1.26 ± 0.39	0.104
Reference diameter (mm)	2.85 ± 0.56	3.00 ± 0.44	0.035
% Diameter Stenosis	52.2 ± 12.7	58.1 ± 11.5	0.001
Adenosine-Bolus	16 (23.9%)	64 (30.5%)	0.353

Values are mean ± SD or n (%); PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; FFR, fractional flow reserve

B. Clinical outcomes at 1 year

For the lesion specific outcome, at 1 year follow-up 4 cases of TLRE (4 cases of FFR-evaluated lesion revascularization and no FFR-evaluated lesion-related myocardial infarction) from 4 patients occurred in the Conservative group. In the PCI group, eight cases of TLRE (8 cases of FFR-evaluated lesion revascularization and 1 case of FFR-evaluated lesion-related myocardial infarction) from 8 patients occurred (Table 3).

For the patient specific clinical outcome, four cases of TLF (1 case of cardiac death, 0 case of FFR-evaluated vessel myocardial infarction and 4 cases of FFR-evaluated lesion revascularization) from 4 patients occurred in the Conservative group and 9 cases of TLF (1 case of cardiac death, 1 case of FFR-evaluated vessel myocardial infarction and 9 cases of FFR-evaluated lesion revascularization) from 9 patients occurred in the PCI group (Table 4).

Five cases of MACE (1 case of death, 0 case of myocardial infarction and 5 cases of target lesion revascularization) occurred in the Conservative group and 13 cases of MACE (4 cases of death, 2 cases of myocardial infarction and 9 cases of target lesion revascularization) occurred in the PCI group (Table 4).

Using Cox proportional hazard model, there was no difference in lesion-related events between Conservative-group and PCI-group (hazard ratio 0.303, 95% CI 0.045-2.025, P = 0.218) (Table 5).

Table 3. Lesion specific outcomes as TLRE at 1 year

	Conservative lesions (n=67)	PCI lesions (n=210)	p value
TLRE	4 (6.0%)	8 (3.8%)	0.449
Target lesion myocardial infarction	0 (0%)	1 (0.5%)	0.571
Target lesion revascularization	4 (6.0%)	8 (3.8%)	0.449

Values are n (%); TLRE, target lesion related events; PCI, percutaneous coronary intervention

Table 4. Patient specific outcomes as TLF and MACE at 1 year

	Conservative group (n=66)	PCI group (n=201)	p value
TLF	4 (6.1%)	9 (4.5%)	0.604
Cardiac death	1 (1.5%)	1 (0.5%)	0.405
Target vessel myocardial infarction	0 (0%)	1 (0.5%)	0.566
Target lesion revascularization	4 (6.1%)	9 (4.5%)	0.604
MACE	5 (7.6%)	13 (6.5%)	0.755
Death	1 (1.5%)	4 (2.0%)	0.805
Myocardial infarction	0 (0%)	2 (1.0%)	0.416
Target lesion revascularization	5 (7.6%)	9 (4.5%)	0.327

Values are n (%); TLF, target lesion failures; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention

Table 5. Cox Proportional Hazard model for TLRE, TLF and MACE at 1 year

	Sig.	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
TLRE Treatment-PCI	0.218	0.303	0.045	2.025
TLF Treatment-PCI	0.253	0.327	0.048	2.222
MACE Treatment-PCI	0.820	0.852	0.215	3.381

TLRE, target lesion related events; TLF, target lesion failures; MACE, major adverse cardiac events; CI, confidence interval; PCI, percutaneous coronary intervention

IV. Discussion

Because measuring FFR evaluates the target lesion functional severity, we intended to evaluate the outcome from that target lesion. Additionally we investigated the clinical outcome affected by the target lesion. So we classified the outcome results into 3 categories. TLRE was lesion specific outcome from the target lesion and MACE was patient specific outcome from the patients. TLF was middle level between TLRE and MACE. The result showed that the difference of outcome between the conservative group and the PCI group was not significant in all types of outcome categories.

The PCI group consisted of more severe stenotic lesions than the conservative group, but showed good trend of lesion events and clinical outcome. The incidence rate of lesion events and clinical outcomes were lower in the PCI group and Cox proportional hazard model revealed hazard ratio of 0.303 for PCI group. But these good trends were not significant.

There are 3 previous similar studies for the patients with gray zone FFR lesions (Lavi et al., 2007; Courtis et al., 2008; Lindstaedt et al., 2010). But, the results were not similar within those studies. One study concluded that deferral of revascularization in patients with gray zone FFR was associated with a higher rate of cardiac events after 1 year although those cardiac events consisted of revascularization (Courtis et al., 2008). The other 2 studies revealed similar findings with this study. The cardiac event rates were similar between the deferred group and the revascularization group (Lavi et al., 2007; Lindstaedt et al., 2010). Interestingly one study revealed that there was no difference in outcome between the Drug eluting stent (DES)-treated group and the deferred group. However, the Bare metal stent (BMS)-treated group showed poor outcome result (Lavi et al., 2007). So in this DES era, that study favor revascularization with DES in lower boundary in gray zone FFR. All 3 studies were not randomized study and not controlled to assign equally in two comparing group like this study.

We could consider several concerns about the result. First, for achievement of maximal hyperemia, there were 3 heterogeneous method of adenosine injection in this study; intravenous adenosine, intracoronary bolus and intracoronary continuous infusion.

Intracoronary adenosine has been adopted by many catheterization laboratories for achievement of maximal hyperemia (Jeremias et al., 2000). Compared with intravenous adenosine, the intracoronary route allows easier administration with fewer systemic adverse effects. But there were some concerns about the suboptimal hyperemia associated with intracoronary adenosine (Jeremias et al., 2000; Casella et al., 2004). But there are studies on higher dose of intracoronary adenosine bolus (Murtagh et al., 2003; Casella et al., 2004) or intracoronary continuous adenosine infusion by using microcatheter which could be useful and safe for inducing optimal hyperemia (Yoon et al., 2009). Due to the difference of FFR measuring protocol between the 4 centers, that could influence the FFR value. Second, the rate of 'hard events' such as cardiac death and myocardial infarction was very low consistently in previous studies about the gray zone FFR lesion as well as this study (Lavi et al., 2007; Courtis et al., 2008; Lindstaedt et al., 2010). Because almost events consisted of revascularization due to angina symptoms in these studies, that suggested the conservative treatment for the gray zone FFR lesion would not make patients increased risk for serious condition. Due to the subjective aspect of symptom, revascularization rate could be variable according to patients group. Third, there was significant difference of baseline characteristics in age, FFR value, location and lesion severity between both groups. The PCI group consisted of more severe stenotic lesions. Considering the good trend of events rate in the PCI group, if the baseline characteristics were similar between the groups, the PCI group would get a significant better event rate and hazard ratio.

From FAME-2 study (De Bruyne et al., 2012), patients in whom at least one stenotic lesion with FFR $\leq$0.80 were randomly assigned to FFR-guided PCI plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical-therapy group). Recruitment was halted prematurely after enrollment of 1220 patients because of a significant between-group difference in the percentage of patients who had a primary endpoint event: 4.3% in the PCI group and 12.7% in the medical-therapy group (hazard ratio with PCI, 0.32; P<0.001). FFR-guided PCI plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the need for urgent revascularization. Difference of primary outcome between the two groups was mainly due to the need for urgent revascularization in the medical-therapy group. And the 'hard events'

such as myocardial infarction, cardiac death occurred similarly. Seeing that the mean FFR measurement in the medical-therapy group was 0.68, the lesions might be causing significant ischemia and therefore the urgent revascularization occurred more frequently during medical therapy.

In DEFER 5-year follow-up study with BMS stent (Pijls et al., 2007), in the lesion with FFR > 0.75, there were similar Cardiac death, AMI and symptom relief between the defer group and the PCI group after 5-year follow up (p=0.52). So the result showed that the lesions with FFR > 0.75 would be defer asymptomatically and safely. The lesions with FFR > 0.75 regardless of treatment type showed better clinical outcome compared to the lesions with FFR > 0.75 (p=0.03). And this study also concluded that the lesions at greatest risk of causing cardiac death or AMI are those that are functionally significant as identified by an FFR < 0.75. Again in this study, mean FFR in the defer group and the PCI group were 0.87 and these group consisted of mainly not-ischemic lesions.

Maybe the patients with gray zone FFR lesions from FAME1/2 and DEFER study would be good candidate for study and would be helpful to comprehend the prognosis of the gray FFR zone lesion.

Because this study was based on retrospective and multi-center registry analysis, it had several inherent limitations. At that time of coronary angiography, decision of whether or not to intervene the lesions with gray zone FFR measurement entirely depended on the operator. Enrolled patients were underwent coronary angiography by many operators in multi-center with various clinical techniques, devices and medication. Therefore, variety of symptoms of patients, angiographic finding and financial problem made the strategies very heterogeneous. We couldn't standardize the reason. One year follow-up period was somewhat short to determine the difference in benefit of strategy, there were a few events from patients and lesions. If the duration was longer enough, the difference of events rate might be significant. And the various routes of adenosine injection could be another limitation influenced the FFR.

Previous 3 studies (Lavi et al., 2007; Courtis et al., 2008; Lindstaedt et al., 2010) regarding clinical outcome of lesions with gray zone FFR didn't show a consistent result about revascularization benefit. That might suggest that uniform treatment strategy for gray zone

FFR is not the best decision. Nevertheless, large randomized control study may be necessary to investigate guidance of cutoff value or angiographic finding or image finding for treatment strategy of lesions with gray zone FFR. It is possible that strategy for lesions with gray zone FFR should be made on a case-by-case basis according to lesion characteristics individually.

V. Conclusion

In coronary lesions with borderline FFR, revascularization did not show the better clinical outcome compared to medical treatment. Therefore, lesions with borderline FFR measurement can be deferred from revascularization without an increased risk for target lesion-related events or MACE, especially for ‘hard events’. But, obviously some patients who have typical angina symptoms refractory to maximal antianginal medical treatment would be considered to take a revascularization.

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– 국문요약 –

경계의 분획혈류 예비력을 가진 환자들에서 재관류술군과 보존적 치료군의 임상경과 비교

목적: 분획혈류 예비력 (FFR)을 재는 것은 심혈관의 협착 정도를 기능적으로 평가하고 치료 계획을 정하는 데에 도움이 되는 방법이다. 여러 연구를 통하여 FFR < 0.75 는 허혈의 유발에 특이적이라고 알려져 있으나 FFR 값이 0.75–0.80 인 병변에 재관류술을 할 것인지 하지 않을 것인지에 대해서는 아직 논란의 여지가 있다. 이 연구의 목적은 경계의 분획혈류 예비력을 가진 환자들에서 재관류술 군과 보존적 치료 군의 임상경과 비교하는 것이다.

방법: 이 연구는 한국의 4 개 병원에서 등록한 FFR 데이터를 이용하여 분석하였다. 총 267 명(평균 62 ± 10 세, 남성 69%)에서 FFR 값이 0.75 에서 0.80 사이인 277 개의 병변(평균 FFR 0.77±0.02)을 분석하였다. 1 년 추적관찰에서의 주요 심장 사건과 FFR 측정 병변 관련 사건의 발생빈도를 분석하였다. 66 명 환자들의 67 개 병변들이 보존적 치료를 받았고 (보존적 치료군) 201 명 환자들의 210 개 병변들이 재관류술을 받았다 (재관류군).

결과: 1 년의 추적 기간 동안 보존적 치료군에서는 4 명의 환자에서 4 건의 FFR 측정 병변 관련 사건이 있었고 (4 건의 FFR 측정 병변 재관류술, 0 건의 FFR 측정 병변 심근경색), 재관류술군에서는 8 명의 환자에서 8 건의 FFR 측정 병변 관련 사건이 있었다 (8 건의 FFR 측정 병변 재관류술, 1 건의 FFR 측정 병변 심근경색).

또한, 보존적 치료군에서 5 건의 주요 심장 사건이 발생 (1 건의 사망, 0 건의 심근경색, 5 건의 FFR 측정 병변 재관류술) 하였고 보존적 치료군에서 13 건의 주요 심장 사건이 발생하였다 (4 건의 사망, 2 건의 심근경색, 9 건의 측정 병변 재관류술).

Cox 비례위험모형을 이용하였을 때 FFR 측정 병변 관련 사건의 발생빈도는 재관류술군과 보존적 치료군 사이에 차이가 없었다 (위험도 0.303, 95% CI 0.045−2.025, P = 0.218).

결론: 경계의 분획혈류 예비력을 가진 병변 들에서 재관류술은 보존적 치료에 비해 좋은 임상경과를 보여주지 못하였다. 따라서 경계의 분획혈류 예비력을 가진 병변들은 FFR 측정 병변 관련 사건의 위험을 증가시키지 않으면서 재관류술을 미룰 수 있겠다.

핵심어: 분획혈류 예비력, 심혈관 협착질환, 재관류술, 보존적 약물치료